Age (<65, ≥65), (<75, ≥75); race (Caucasian, Non-Caucasian); gender (male, female); hypertension (yes, no); diabetes mellitus (yes, no); BMI (<30, ≥30 kg/m^2); baseline TG (<200, ≥200 mg/dl); baseline LDL-C (<160, ≥160 mg/dl); baseline HDL-C (<35, ≥35 mg/dl), (<40, ≥40 mg/dl); known CHD (yes, no); family history of CHD (yes, no).

In study P00474 and in the pooled monotherapy studies, the response to ezetimibe 10 mg was consistent across all subgroups, including race (Caucasian vs. Non-Caucasian). However, additional post-hoc subgroup analyses by race demonstrated decreased LDL-C response over time in Asian subjects receiving ezetimibe (pooled monotherapy: n= 15 and study P00474, n= 7). In study P00475, two interactions were significant: baseline direct LDL-C by treatment (p= 0.020) and race by treatment (p= 0.049). The respective ezetimibe treatment differences by race relative to placebo were -10.4% for Non-Caucasians and –17.8% for Caucasians. Race was unbalanced with very few subjects in the Non-Caucasian category (60/628 in ezetimibe and 15/210 in placebo). Additional post-hoc subgroup analyses, demonstrated diminished LDL-C responses over time in Asian (n= 8) and Hispanic (n= 23) subjects receiving ezetimibe in this study.

Percent Change in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint Examined by Race: Intent-to-Treat Data Set

Treatment by Race	N	Mean[a]	Difference in Means	Median (Range)
P00474:				
Caucasian:				
Placebo	177	0.2		-0.4
Ezetimibe 10 mg	550	-18.1		-18.0
[Ezetimibe] – [Placebo]			-18.3	
Non-Caucasian:				
Placebo	22	1.4		-1.4
Ezetimibe 10 mg	56	-17.8		-18.5
[Ezetimibe] – [Placebo]			-19.2	
P00475:				
Caucasian:				
Placebo	195	0.6		0.4
Ezetimibe 10 mg	568	-17.2		-18.1
[Ezetimibe] – [Placebo]			-17.8	
Non-Caucasian:				
Placebo	15	-3.2		-3.0
Ezetimibe 10 mg	60	-13.6		-14.7
[Ezetimibe] – [Placebo]			-10.4	

a= raw mean percent changes from baseline

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Subgroup Analysis for P00474:

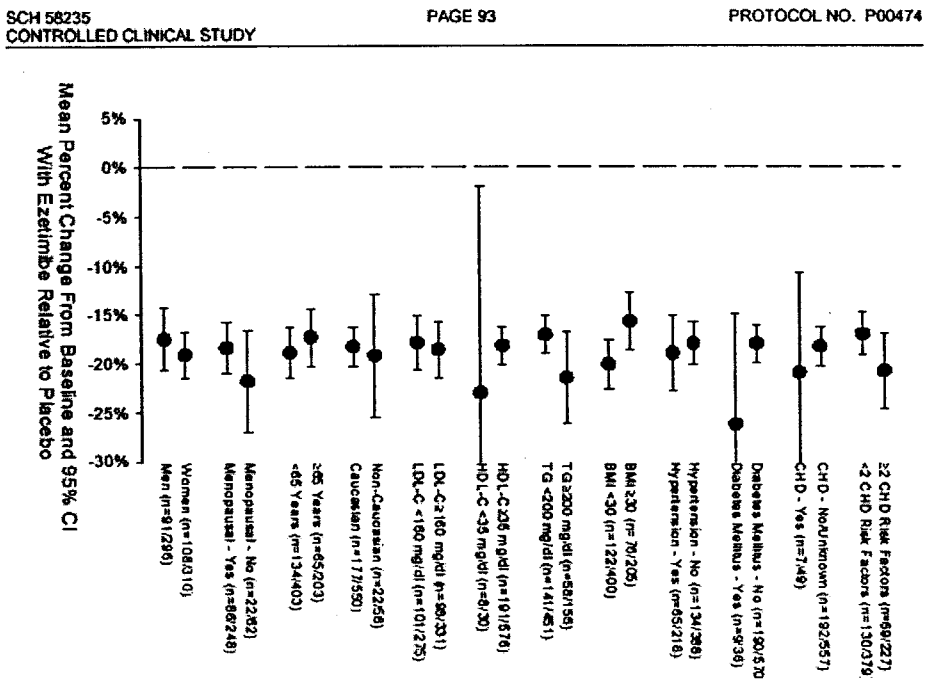

Figure 4 Point estimate and 95% confidence interval of the difference between response (raw mean percent change from baseline) to ezetimibe 10 mg and placebo in direct LDL-C in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set.

Source Data: **Section 14.2.2.1.5.1.** and **Section 14.2.2.1.5.2.**. In subgroup labels, n=X/Y indicates the number of subjects treated with placebo (X)/number treated with ezetimibe (Y). Means represent raw means, except for the "overall," which is a least-square mean from the statistical model.

Subgroup Analysis for P00475:

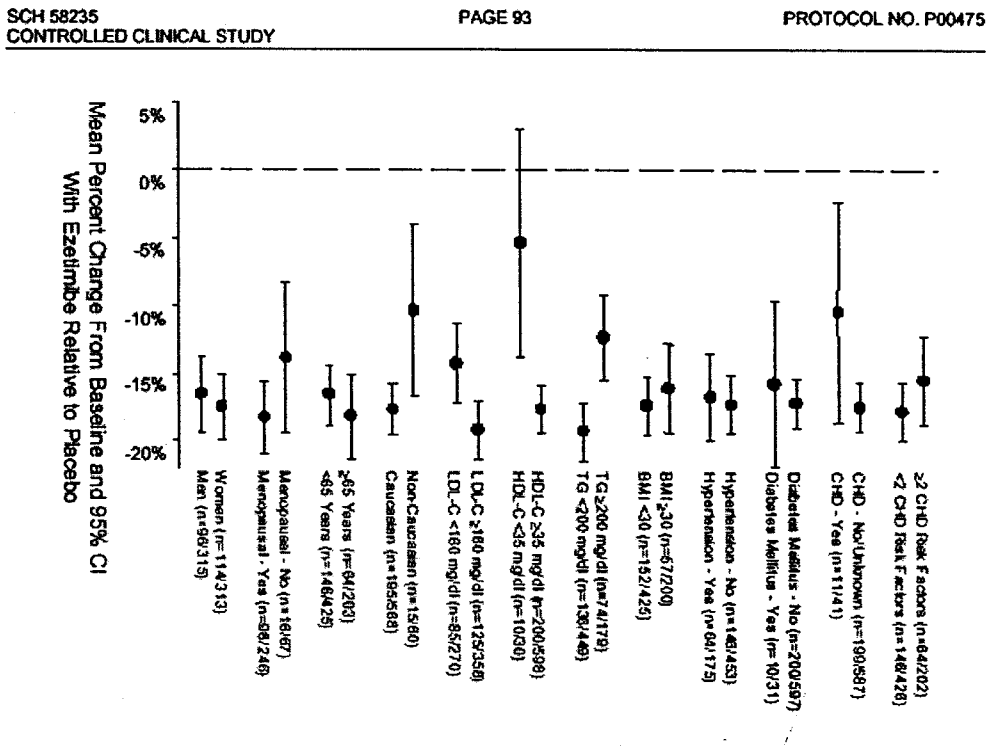

Figure 4 Point estimate and 95% confidnce interval of the difference between response (raw mean percent change from baseline) to ezetimibe 10 mg and placebo in direct LDL-C in various subgroups of the population defined by baselinecharacteristics: Intent-to-Treat Data Set.

Source Data: **Section 14.2.2.1.5.1.** and **Section 14.2.2.1.5.2..** In subgroup labels, n=X/Y indicates the number of subjects treated with placebo (X)/number treated with ezetimibe (Y).

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Subgroup Analysis for P00474 + P00475:

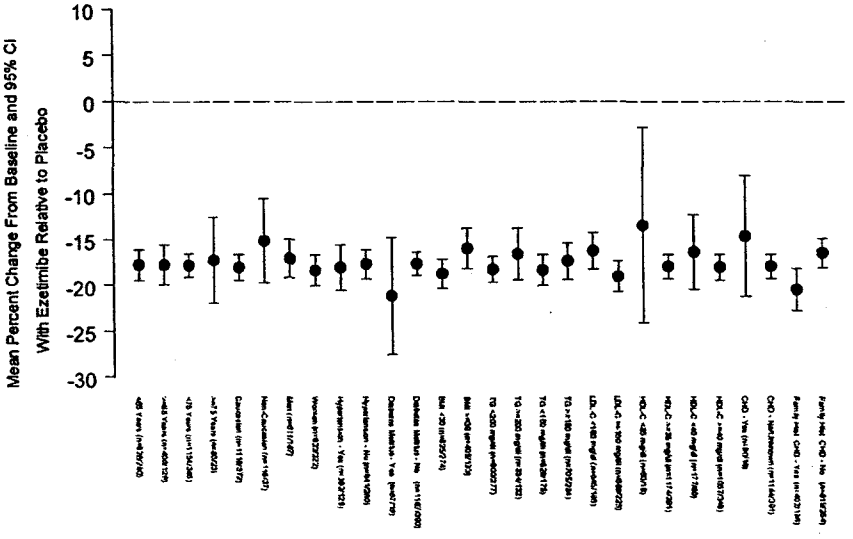

Figure 2 Point estimate and 95% confidence interval of the difference in response (raw mean percent change from baseline) between Ezetimibe and placebo in direct LDL-C in various subgroups of the population defined by baseline characteristics: Phase III Monotherapy Studies (Intent-to-Treat Data Set).
(Appendix 10)

Factorial Co-Administration Studies:

The subgroup analyses were the same as for the monotherapy studies with the following exceptions. In the factorial studies, only age <65 and ≥65 years was evaluated and, for TG, another subgroup was added: <150 and ≥150 mg/dl (ATP III cut-off).

Subgroup analyses for the 4 pooled Factorial Coadministration Studies generally showed consistency of treatment effect across all subgroups examined with the exception of an observed race difference in the LDL-C response to coadministration therapy between Caucasians compared with Non-Caucasians:

Mean Percent Change (SEM) in Plasma Concentration of Direct LDL-C Between baseline and Endpoint: Factorial Coadministration Studies-Subgroup Analysis (Intent-to-Treat Data Set)

Race	N	All Statin	N	Ez + All Statin	[Ez + Statin] – [All Statin] 95% CI
Caucasian	807	-32.2 (0.6)	803	-46.9 (0.6)	-14.6 (-16.2, -13.0)
Non-Caucasian	120	-34.3 (1.6)	111	-40.9 (2.0)	-6.6 (-11.6, -1.6)

As demonstrated in the above table, there was a treatment difference in the LDL-C response to coadministration therapy between Caucasians and Non-Caucasians. When coadministered with statin, ezetimibe produced an additional 14.6% reduction in LDL-C in Caucasians compared to statin alone. In Non-Caucasians the incremental benefit was 6.6%.

The following tables depict the mean percent change in plasma concentration of direct LDL-C between baseline and endpoint by race for each of the 4 Factorial Studies:

LOVASTATIN:

Percent Change (Mean and Median) in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Lovastatin Factorial Study (P00679): Intent-to-Treat Data Set Examined By Race: Pooled Treatment Groups

Treatment	N		Mean		Difference in Means		Median	
	Race							
	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C
Placebo	58	5	0.8	-9.4			0.0	-15.3
Ezetimibe 10 mg	59	12	-18.1	-20.9			-19.3	-18.3
[Ezetimibe] – [Placebo]					-18.9	-11.5		
All Lova	196	22	-24.7	-25.0			-25.7	-24.8
Ez 10 + All Lova	165	25	-39.3	-37.3			-41.8	-40.3
[Ez + All Lova] – [All Lova] (95% CI)					-14.6 (-17.7, -11.6)	-12.3 (-20.5, -4.2)		

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SIMVASTATIN:

Percent Change (Mean and Median) in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Simvastatin Factorial Study (P00680): Intent-to-Treat Data Set Examined By Race: Pooled Treatment Groups								
Treatment	N		Mean		Difference in Means		Median	
	Race							
	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C
Placebo	66	3	-1.0	-7.8			0.2	-0.2
Ezetimibe 10 mg	56	3	-18.4	-12.1			-19.9	-7.4
[Ezetimibe] – [Placebo]					-17.4	-4.3		
All Simva	235	26	-35.8	-37.1			-38.4	-38.4
Ez 10 + All Simva	242	26	-50.8	-40.3			-53.3	-49.1
[Ez + All Simva] – [All Simva] (95% CI)					-14.98 (-17.7, -12.3)	-3.19 (-14.9, +8.5)		

PRAVASTATIN:

Percent Change (Mean and Median) in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Pravastatin Factorial Study (P00691): Intent-to-Treat Data Set Examined By Race: Pooled Treatment Groups								
Treatment	N		Mean		Difference in Means		Median	
	Race							
	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C
Placebo	49	13	0.6	4.1			0.2	3.4
Ezetimibe 10 mg	60	3	-18.9	-15.3			-19.6	-15.6
[Ezetimibe] – [Placebo]					-19.5	-19.3		
All Prava	172	31	-24.4	-24.6			-24.9	-25.6
Ez 10 + All Prava	176	28	-38.3	-33.5			-39.3	-37.4
[Ez + All Prava] – [All Prava] (95% CI)					-13.9 (-16.6, -11.3)	-8.9 (-17.0, -0.8)		

ATORVASTATIN:

Percent Change (Mean and Median) in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Atorvastatin Factorial Study (P00692): Intent-to-Treat Data Set Examined By Race: Pooled Treatment Groups								
Treatment	N		Mean		Difference in Means		Median	
	Race							
	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C	Cauc	Non-C
Placebo	49	11	6.4	3.3			6.0	3.1
Ezetimibe 10 mg	57	8	-19.5	-10.7			-18.9	-7.8
[Ezetimibe] – [Placebo]					-25.9	-14.0		
All Atorva	204	41	-42.0	-44.9			-44.5	-48.8
Ez 10 + All Atorva	220	32	-55.0	-50.6			-57.8	-57.7
[Ez + All Atorva] – [All Atorva]					-12.99 (-15.9, -10.0)	-5.76 (-14.7, +3.2)		

Comments on the above tables:

Note the small number of Non-Caucasians compared to Caucasians and the large placebo effect in Non-Caucasians in the lovastatin and simvastatin studies which confounds interpretation of the differences in efficacy between the races.
Except for pravastatin, the effect of ezetimibe relative to placebo on LDL-C reduction was reduced in Non-Caucasians compared to Caucasians.
Also, the LDL-C response was reduced in Non-Caucasians compared to Caucasians when ezetimibe was coadministered with statin. This racial difference in response was statistically significant in the simvastatin (p= 0.002) and atorvastatin (p= 0.011) factorial studies.

The following post-hoc analysis demonstrates diminished LDL-C lowering efficacy of coadministration therapy in Black subjects:

Mean % Change (SEM) in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Factorial Coadministration Studies- Subgroup Analysis (Intent-to-Treat Data Set)					
Race	N	All Statin	N	Ez + All Statin	[Ez + Statin] – [All Statin] 95% CI
Caucasian	807	-32.2 (0.6)	803	-46.9 (0.6)	-14.6 (-16.2, -13.0)
Non-Caucasian: Black Others	**120:** 56 64	**-34.3 (1.6):** -35.8 -33.0	**111:** 43 68	**-40.9 (2.0)** -34.5 -45.0	**-6.6 (-11.6, -1.6)** +1.3 (-6.1, +8.7) -12.0 (-18.8, -5.2)

The results of additional post-hoc analyses by racial/ethnic group, requested in a teleconference on September 5, 2002 between FDA (Dr. Stadel, Dr. Choudhury, Mr. Koch and myself) and the sponsor, are discussed below.

Asian and Black subjects receiving coadministration therapy demonstrated diminished mean LDL-C response compared to Caucasians in the pooled Factorial Studies (treatment difference between coadministration and statin alone for the mean percent change in LDL-C from baseline to endpoint):
Asians (n= 18): ~+3.5%; Blacks: +1.3% (n= 44); Caucasians: -14.6% (n= 813).

These treatment differences were most evident in the atorvastatin factorial study in which the treatment difference between ezetimibe/atorva and atorva alone in the mean percent change in LDL-C from baseline to endpoint was ~+15% and ~+5% in Black (n= 9) and Asian (n= 6) subjects, respectively, compared to a mean change of -13% in Caucasians (n= 222) enrolled in this study.

Other particularly notable racial treatment differences were present between Black and Caucasian subjects receiving ezetimibe with simvastatin where the change in mean LDL-C was ~+3% in Blacks (n= 11) and was –15% in Caucasians (n= 248). In Asians receiving ezetimibe with pravastatin (n= 5), there was no change in mean LDL-C compared to pravastatin alone but there was an ~14% reduction in Caucasians (n= 176).

In addition, the LDL-C response diminished over time in Black and Asian subjects being most evident when all the Factorial Studies were pooled, in the atorvastatin factorial study, in the simvastatin study (Blacks only) and the pravastatin study (Asians only).

The small numbers of Non-Caucasians enrolled in these studies confounds interpretation of these results. A study is needed with an adequate sample size of Non-Caucasians to further evaluate racial/ethnic variations in LDL-C response to ezetimibe.

The following figures demonstrate the mean percent change from baseline in direct LDL-C in subgroups defined by subject baseline charactristics for each Factorial Study.

P00679 (Lovaststin): see Figure below:

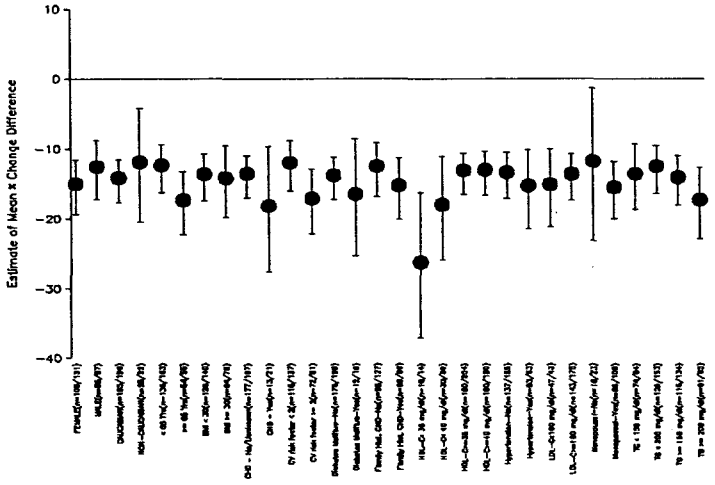

Figure 4 Point estimate and 95% confidence interval of the difference in response (raw mean percent change from baseline) between Ezetimibe+All Lovastatin (pool of all doses of lovastatin coadministered with ezetimibe 10 mg) and All Lovastatin (pool of all doses of lovastatin) in direct LDL-C in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set.
In subgroup labels, n=X/Y indicates the number of subjects treated with ezetimibe plus lovastatin (X)/number of subjects treated with lovastatin alone (Y). Source Data: **Section 14.2.2.1.6.**

P00680 (Simvastatin): see Figure below:

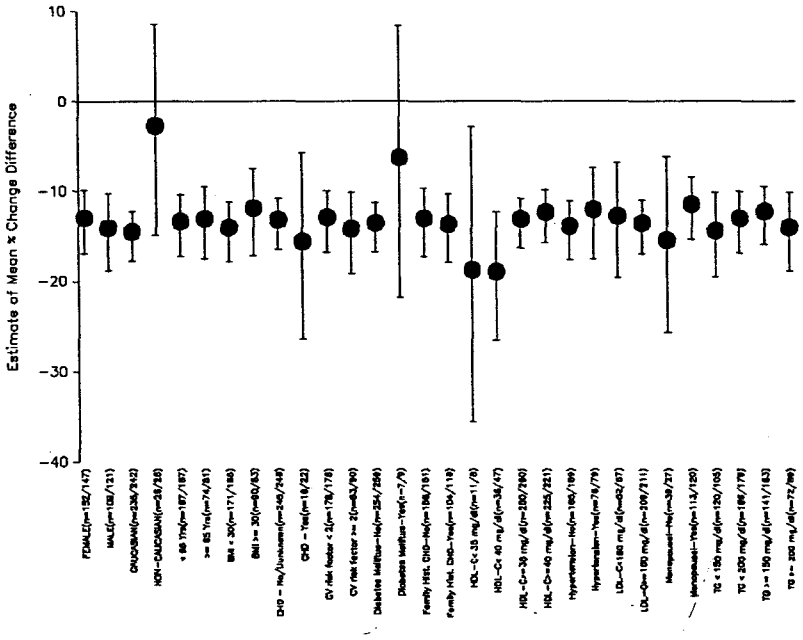

Figure 4 Point estimate and 95% confidence interval of the difference in mean percent change between the two treatment pools in direct LDL-C in various subgroups defined by baseline characteristics: Intent-to-Treat.

In subgroup labels, n=X/Y indicates the number of subjects treated with simvastatin alone (X)/number of subjects treated with ezetimibe plus simvastatin (Y). Source Data: **Section 14.2.2.1.6.2.**

P00691 (Pravastatin): see Figure below:

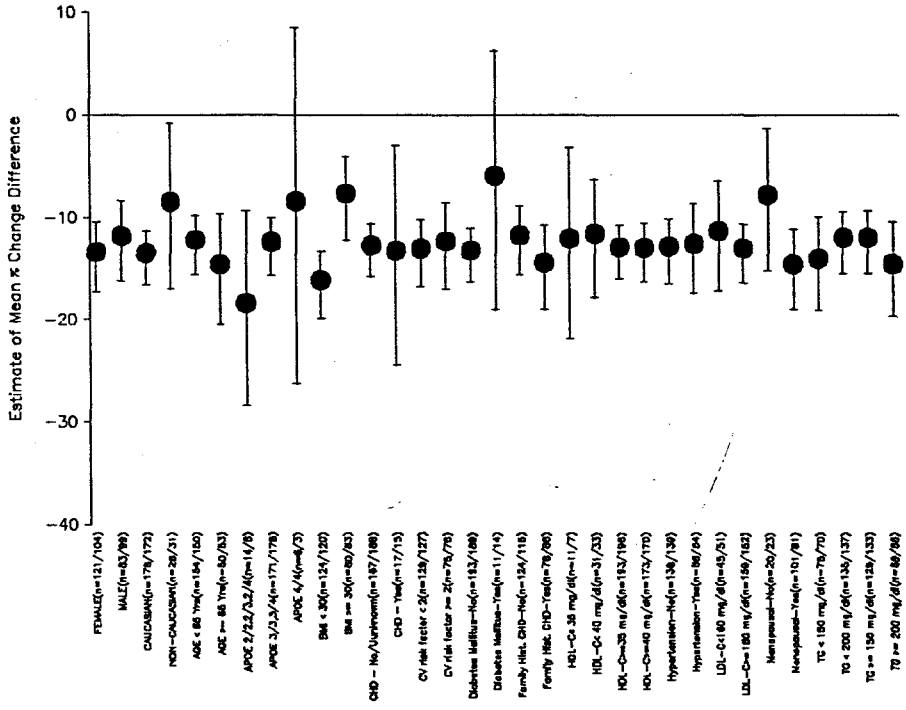

Figure 4 Point estimate and 95% confidence interval of the difference in response (raw mean percent change from baseline) between Ezetimibe+All Pravastatin (pool of all doses of pravastatin coadministered with ezetimibe 10 mg) and All Pravastatin (pool of all doses of pravastatin) in direct LDL-C in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set.
In subgroup labels, n = X/Y indicates the number of subjects treated with ezetimibe plus pravastatin (X)/number of subjects treated with pooled pravatstatin alone (Y). *Source Data:* **Section 14.2.2.1.6.**

P00692 (Atorvastatin): see Figure below:

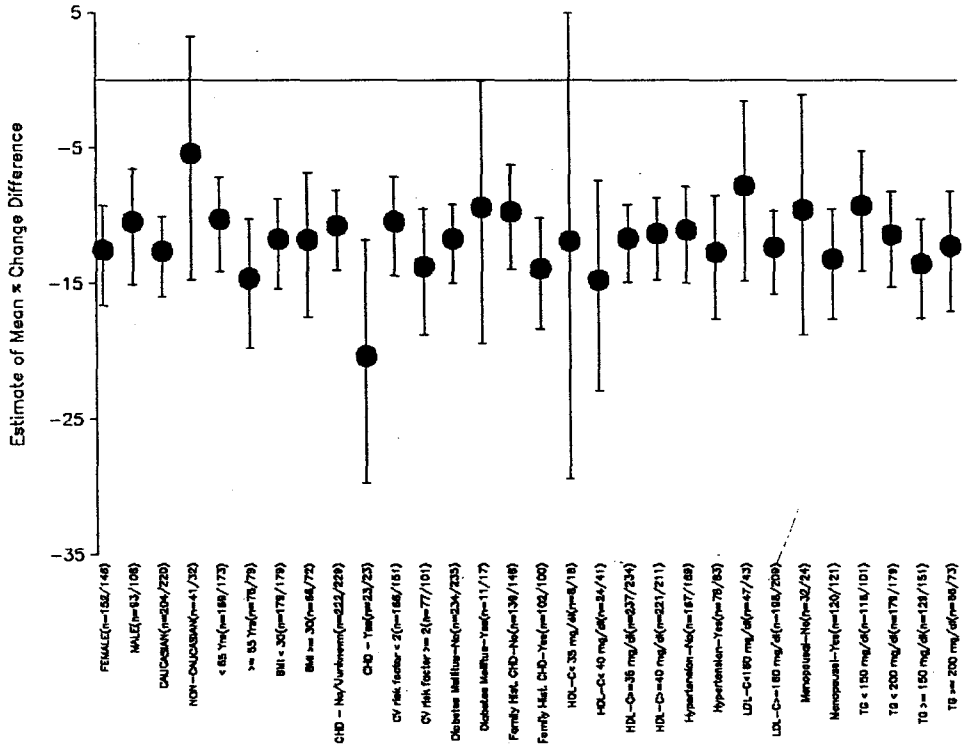

Figure 4 Point estimate and 95% confidence interval of the difference in response (raw mean percent change from baseline) between Ezetimibe+All Atorvastatin (pool of all doses of atorvastatin coadministered with ezetimibe 10 mg) and All Atorvastatin (pool of all doses of atorvastatin) in direct LDL-C in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set.

In subgroup labels, n=X/Y indicates the number of subjects treated with ezetimibe plus atorvastatin (X)/number of subjects treated with atorvastatin alone (Y). Source Data: **Section 14.2.2.1.6.**.

Add-On Study (P02173):
Summary statistics for the primary efficacy variable were provided for the following groups: gender (male, female), age (<65 years, ≥65 years)/(<75 years, ≥75 years), race (Caucasian, Non-Caucasian), NCEP ATP II category, BMI (<25, 25-30, 30-40, ≥40 kg/m^2), and waist circumference (high: >102 cm for men and >88 cm for women), low: ≤102 cm for men, ≤88 cm for women).

With the exception of race, the results of the subgroup analysis indicate that the response to ezetimibe 10 mg added to ongoing statin therapy was generally consistent across subgroups. However, as the following table demonstrates, there was a treatment difference in the LDL-C response between Caucasians and Non-Caucasians. Per Dr. Japo Choudhury, the stastical reviewer, this treatment difference was significant (p = 0.056).

Percent Change in Calculated LDL-C Between Baseline and Endpoint Examined by Race: Intent-to-Treat Data Set

Race	N	Mean[a]	SD	Median	Min	Max
Caucasian:						
Statin + Placebo	354	-3.4	13.7	-3.4	-49.3	47.4
Statin + Ezetimibe 10 mg	336	-25.4	14.1	-27.0	-69.9	63.3
Non-Caucasian						
Statin + Placebo	34	-9.1	12.0	-10.2	-34.6	24.4
Statin + Ezetimibe 10 mg	39	-24.4	19.0	-26.4	-57.1	37.9

a= arithmetic mean % change from baseline

Comment on the above table:
Ezetimibe added to ongoing statin therapy resulted in an additional 22% reduction in mean LDL-C concentration in Caucasians (95% CI: -24.1, -19.9) compared to an additional 15.3% reduction in Non-Caucasians (95% CI: -22.9, -7.8).

Additional post-hoc subgroup analyses by race demonstrated diminished mean LDL-C response over time in Black (n= 27), Asian (n= 5) and Hispanic (n= 8) subjects receiving ezetimibe with statin compared to Caucasian subjects (n= 336).

The following table demonstrates the mean percent change from baseline in calculated LDL-C in the various subgroups in the Add-On Study:

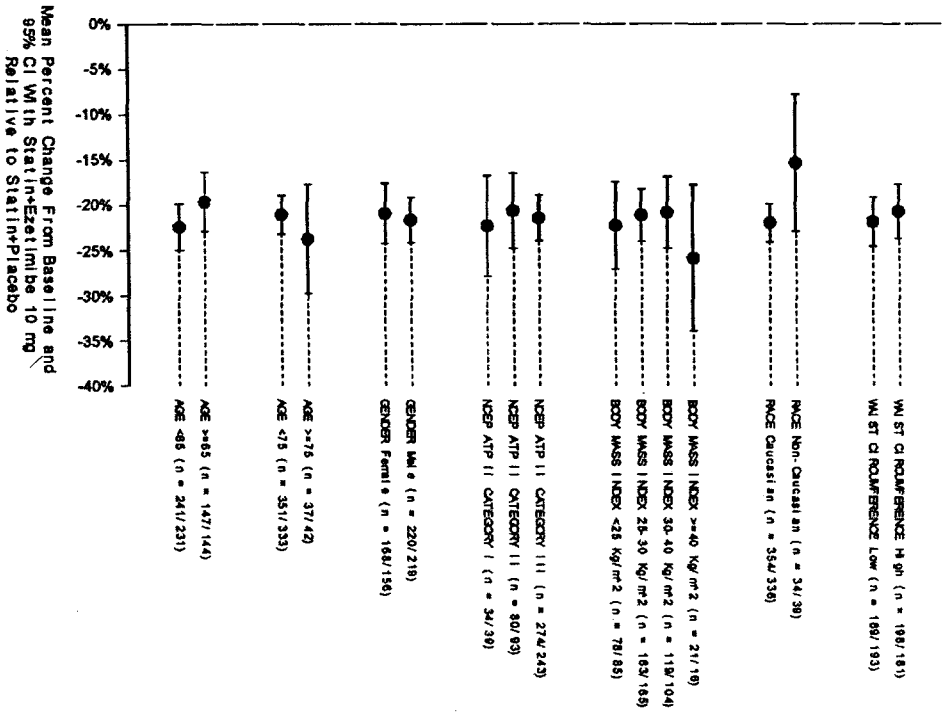

Figure 2 Point estimate and 95% confidence interval of the difference between response (raw mean percent change from baseline) to statin + ezetimibe and statin + placebo in calculated LDL-C, overall and in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set

Source Data: **Section 14.2.2.1.4.1.1.** and **Section 14.2.2.1.4.1.2.**. In subgroup labels, *n = X/Y* indicates the number of subjects treated with statin + placebo (X)/number of subjects treated with statin + ezetimibe 10 mg (Y).

Overall Effect of Black Race on Mean Percent Change From Baseline to Endpoint in Calculated LDL-C Over Time (Difference in Medians): in the Pooled Phase III Monotherapy Studies, the Pooled Factorial Studies and the Add-On Study (Intent-to-Treat Data Set):

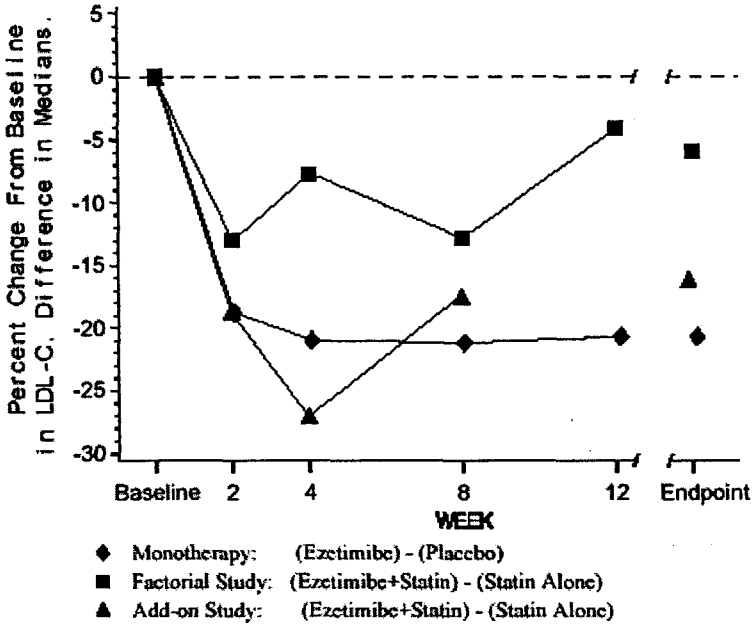

Figure 3 Percent Change from Baseline in Calculated LDL-C in Black Subjects over time (difference in medians): in the Factorial Coadministration Studies, the Add-On Study, and the Pooled Phase III Monotherapy (Intent-to-Treat Data Set)

Comment on the above figure:
Post-hoc subgroup analyses suggested a diminished LDL-C response with coadministration in Black subjects from week 8 to week 12 in the pooled Factorial Studies and from week 4 to week 8 in the Add-On Study. However, efficacy was maintained over 12 weeks in the pooled Phase III Monotherapy Studies.

The following table demonstrates the same point:

Table 21 Median Percent Change in Plasma Concentration of Low-Density-Lipoprotein (Calculated LDL-C) Between Baseline and Endpoint: Subgroup Analysis for Black Race: Factorial Coadministration Studies, Phase III Monotherapy Studies, and Add-On Study (Intent-to Treat Data Set)

	Pooled Factorial Coadministration Studies				Add-On Study		Phase III Monotherapy	
	Placebo	EZ	All Statin	EZ + All Statin	All Stain	EZ + All Statin	Placebo	EZ
Baseline	(n=15)	(n=11)	(n=56)	(n=44)	(n=19)	(n=27)	(n=21)	(n=69)
Median	171.0	186.7	179.8	176.7	135.5	122.5	154.3	160.7
Week 2	(n=15)	(n=10)	(n=53)	(n=43)	(n=18)	(n=23)	(n=21)	(n=65)
Median	179.0	152.5	123.0	99.0	120.0	92.0	167.0	134.0
Median Percent Change from Baseline	-0.4	-20.8	-29.1	-42.1	-9.6	-28.3	0.9	-17.9
Difference in Median Percent Change		NA		-13.0		-18.7		-18.8
Week 4	(n=15)	(n=10)	(n=55)	(n=41)	(n=19)	(n=23)	(n=20)	(n=65)
Median	171.0	153.0	116.0	99.0	125.0	83.0	155.0	132.0
Median Percent Change from Baseline	-2.4	-20.3	-36.8	-44.5	-7.0	-34.1	0.3	-20.6
Difference in Median Percent Change		NA		-7.7		-27.0		-21.0
Week 8	(n=14)	(n=10)	(n=53)	(n=38)	(n=17)	(n=23)	(n=21)	(n=60)
Median	174.0	146.5	117.0	93.0	119.0	95.0	156.0	130.0
Median Percent Change from Baseline	-0.3	-21.1	-34.5	-47.4	-10.2	-27.7	1.1	-20.2
Difference in Median Percent Change		NA		-12.8		-17.5		-21.2
Week 12	(n=14)	(n=9)	(n=50)	(n=35)	NA[a]	NA	(n=19)	(n=57)
Median	176.0	147.0	110.5	107.0	NA	NA	170.0	132.0
Median Percent Change from Baseline	-0.4	-15.7	-39.1	-43.2	NA	NA	1.8	-18.9
Difference in Median Percent Change		NA		-4.1		NA		-20.7
Endpoint	(n=15)	(n=10)	(n=56)	(n=43)	(n=19)	(n=24)	(n=21)	(n=68)

Table 21 Median Percent Change in Plasma Concentration of Low-Density-Lipoprotein (Calculated LDL-C) Between Baseline and Endpoint: Subgroup Analysis for Black Race: Factorial Coadministration Studies, Phase III Monotherapy Studies, and Add-On Study (Intent-to Treat Data Set)

	Pooled Factorial Coadministration Studies				Add-On Study		Phase III Monotherapy	
	Placebo	EZ	All Statin	EZ + All Statin	All Stain	EZ + All Statin	Placebo	EZ
Median	178.0	149.5	114.5	110.0	119.0	97.0	166.0	135.0
Median Percent Change from Baseline	3.6	-15.4	-36.2	-42.1	-11.7	-27.8	1.8	-18.9
Difference in Median Percent Change		NA		-5.9		-16.1		-20.7

a: Study was only 8 weeks.

(See Appendix 11 of the ISE

Note: the second section of the above table refers to the values at endpoint.

The above data triggered a teleconference on September 5, 2002 between FDA (Dr. Stadel, Dr. Choudhury, Mr. Koch and myself) and the sponsor to request graphs similar to those generated

for Black subjects, for the following groups: Caucasians, Non-Caucasians and each racial/ethnic group enrolled in non-Caucasian subgroup for the following studies: Factorial Studies pooled and individually by study, Monotherapy Studies pooled and individually by study and the Add-On Study. These results have already been discussed above.

Familial Homozygous Hypercholesterolemia (P01030):
Results of the primary efficacy variable, percent change from baseline in direct LDL-C, were examined in the following subgroups: sex, age, race, LDL-C, HDL-C, TG, hypertension, diabetes mellitus, BMI, known CHD, previous apheresis/plasmapheresis, concomitant apheresis/plasmapheresis, genotyping diagnosis, and estimated LDL-receptor residual activity.

The sponsor concluded that although in some of the subgroups the number of subjects was small, the results of these analyses generally indicated that the overall increase in response resulting from the addition of ezetimibe 10 mg to statin monotherapy was consistent across most subgroups. However, the results of these subgroup analyses should be interpreted with caution given the small sample size, in some cases, there were only 1-5 subjects with a given characteristic in a given subgroup.

The sponsor also analyzed the effect of concomitant apheresis and LDL-receptor residual activity on the results of the primary efficacy variable. The sponsor concluded, based on the following table, that subjects receiving eze + statin had a greater mean % change from baseline to endpoint in direct LDL-c compared to statin alone regardless of concomitant apheresis administration. They also stated that subjects with an estimated LDL-receptor residual activity of <5% had similar reductions in LDL-C concentrations resulting from the addition of ezetimibe 10 mg to statin monotherapy. However, the response was greater in the combination therapy group when receptor activity was ≥5%. Again, these observations should be interpreted with caution due to the small sample sizes.

% Change from Baseline to Endpoint: Direct LDL-c:							
	Stain 80 mg			Eze + Statin 40/80			Difference
	N	Mean	SEM	N	Mean	SEM	Point Est 95%CI
Conc apheresis							
Yes	8	-6.6	2.3	17	-12.6	4.5	-5.9 (-15.9, 4.0)
No	9	-4.9	5.0	16	-27.2	4.0	-22.3 (-35.0, -9.7)
Residual activity							
<5%	4	-3.8	2.8	4	-3.8	15.0	-0.0 (-30.0, 29.9)
≥5%	2	11.6	2.0	6	-32.4	5.2	-44.1(-55.0, -33.1)

Homozygous Sitosterolemia:
The sponsor examined the results of the primary efficacy variable for various subgroups: stratum (concomitant usage of bile salt binding resins), concomitant usage of statins, gender, protocol site (U.S. vs. outside the U.S.), LDL (higher or lower than baseline median values) and sitosterol (higher or lower than baseline median values). The sponsor concluded that the response to ezetimibe was consistent across subgroups. In particular, neither concomitant resin nor statin therapy altered the response to ezetimibe. These results should be interpreted with caution due to

the small sample sizes (in some cases, there were only 1-8 subjects with a given characteristic in a given subgroup).

C. Evaluation of Pediatric Program

At the April 25, 2001 pre-NDA meeting, the Sponsor requested, and FDA approved, a waiver for pediatric patients ≤ 10 years of age (since they are not generally treated for hypercholesterolemia) and a deferral for patients ≥ 10 years of age (since efficacy and safety data for ezetimibe coadministered with statins were not available until late in the clinical program).

[ ]

On November 1, 2001, FDA issued a letter to the sponsor stating that a Written Request could not be issued before completion of the review of the NDA.

D. Comments on Data Available or Needed in Other Populations

Patients With Hepatic Insufficiency:
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe increased ~1.7-fold in patients with mild hepatic insufficiency compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC for total ezetimibe was increased ~4-fold on day 1 and day 14 compared to healthy subjects. Therefore, the sponsor does not recommend that ezetimibe be used in patients with moderate orsevere hepatic insufficiency.

Patients With Renal Insufficiency:
A single 10mg dose of ezetimibe was administered to 9 healthy subjects and to 8 patients with severe renal disease (CrCl ≤ 30 ml/min). The mean AUC for total ezetimibe was increased ~1.5-fold in renally impaired patients compared to healthy subjects. The result was not considered clinically significant. Therefore, no dosing adjustments are recommended for renally impaired patients.

Efficacy Data in Non-Caucasians:
Due to insufficient enrollment of Non-Caucasian subjects, a study is recommended to further evaluate the racial/ethnic variation in efficacy of Zetia as

monotherapy and when coadministered with statin. The timing of this study in relation to approval of Zetia requires discussion at the Division and Office levels.

X. Conclusions and Recommendations

A. Conclusions

Efficacy conclusions have been previously summarized. Please refer to the Review Summary on the cover sheet of this review; the Executive Summary; section VI.A., Brief Statement of Conclusions; and section VI.D. Efficacy Conclusions.

B. Recommendations

This reviewer recommends approval of Zetia for the following indications:

Primary Hypercholesterolemia:
Zetia administered alone or with an HMG-CoA reductase inhibitor and as an adjunct to diet for the reduction of elevated LDL-C, TC and Apo B.

Homozygous Familial Hypercholesterolemia:
Zetia administered with atorvastatin or simvastatin for the reduction of elevated LDL-C and TC, as an adjunct to other lipid-lowering therapy.

Homozygous Sitosterolemia:
Zetia as adjunctive therapy for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Draft labeling recommendations are appended to this review.

In addition, a study is recommended to further evaluate the racial/ethnic variation in efficacy of Zetia as monotherapy and when coadministered with statin.The timing of this study in relation to approval of Zetia requires discussion at the Division and Office levels.

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XI. Appendix

A. Other Relevant Materials

Individual Efficacy Data for the Phase II Studies:

C96-411 and C96-345:

Table 1
Percent Changes (S.E.M.) From Baseline to Treatment Endpoint
in Plasma Concentrations of Various Lipid-Related Variables in the Intent-to-Treat Data Set

		SCH 58235					Lovastatin
	Placebo	mg	mg	10 mg	mg	mg	40 mg
Variables	(n=17)	(n=17)	(n=20)	(n=18)	(n=16)	(n=18)	(n=18)
Direct LDL-C	+3.8 (2.5)	-14.6 (2.4)	-15.7 (1.6)	-16.4 (2.2)	-17.9 (2.0)	-20.0 (2.0)	-31.8 (2.8)
Calculated LDL-C	+1.3 (2.5)	-16.0 (2.4)	-18.0 (1.4)	-17.6 (2.2)	-19.8 (2.2)	-22.1 (2.1)	-33.2 (2.6)
Apolipoprotein B	+3.4 (1.6)	-12.5 (2.5)	-13.5 (2.0)	-7.9 (3.4)	-13.5 (2.2)	-12.5 (2.6)	-25.3 (3.1)
HDL-C	+4.4 (2.6)	+4.6 (1.7)	+3.8 (2.0)	+4.4 (3.3)	+2.5 (2.7)	+1.8 (2.5)	+7.1 (2.1)
HDL_2-C	+0.4 (8.6)	+7.5 (6.0)	-1.9 (5.1)	+13.7 (10.0)	+1.3 (6.5)	-0.1 (6.5)	+14.9 (5.4)
HDL_3-C	+6.8 (3.4)	+3.3 (3.8)	+5.6 (3.0)	+2.7 (4.6)	+8.8 (4.9)	+7.4 (4.3)	+4.1 (3.3)
Apolipoprotein A_1	-0.6 (2.0)	+4.6 (1.9)	+2.3 (2.0)	+9.6 (2.7)	+0.9 (2.7)	+3.4 (2.6)	+4.4 (2.1)
Total Cholesterol	+0.9 (2.1)	-10.3 (1.8)	-11.8 (1.2)	-10.4 (1.9)	-14.2 (1.9)	-15.8 (1.8)	-22.8 (2.3)
Triglycerides	-6.4 (5.2)	-0.9 (5.3)	+2.9 (7.0)	+13.1 (9.4)	-7.8 (5.3)	-8.3 (4.6)	-15.4 (5.6)
Lipoprotein(a)	+1.9 (7.8)	-2.6 (6.1)	-1.3 (4.6)	0.0 (7.5)	-8.9 (7.2)	+7.3 (5.2)	-4.7 (4.5)

S.E.M. = standard error of the mean.
Not every subject had an end-of-treatment measurement for every variable; "n" sizes varied from 15 to 20.

C98-010:

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Table 1
Percent Changes (S.E.M.) From Baseline to Study Endpoint in Plasma Concentrations of Various Lipid-Related Variables in the Intent-to-Treat Data Set

		SCH 58235			
Variables	Placebo (n=52)	mg (n=47)	mg (n=49)	mg (n=49)	10 mg (n=46)
Direct LDL-C	+4.3 (1.4)	-9.9 (1.5)	-12.6 (1.5)	-16.4 (1.4)	-18.7 (1.5)
Calculated LDL-C	+3.6 (1.4)	-9.3 (1.5)	-13.9 (1.5)	-18.4 (1.5)	-18.9 (1.5)
Apolipoprotein B	+2.4 (1.6)	-6.3 (1.7)	-11.7 (1.7)	-15.1 (1.6)	-15.2 (1.7)
HDL-C	+2.2 (1.4)	+4.1 (1.5)	+2.8 (1.4)	+2.7 (1.4)	+4.5 (1.5)
HDL_2-C	+16.1 (5.9)	+15.0 (6.4)	+10.4 (6.3)	+16.9 (6.1)	+11.7 (6.5)
HDL_3-C	-0.1 (2.7)	+2.6 (2.9)	-2.2 (2.8)	-0.7 (2.7)	-0.2 (2.9)
Apolipoprotein A_1	-2.9 (1.7)	+1.2 (1.8)	-2.9 (1.8)	-1.6 (1.7)	+0.7 (1.8)
Total Cholesterol	+2.2 (1.1)	-6.8 (1.2)	-10.3 (1.2)	-12.6 (1.1)	-12.6 (1.2)
Triglycerides	-2.9 (3.7)	-7.7 (4.0)	-10.4 (3.9)	-5.4 (3.8)	-3.8 (4.0)
Lipoprotein(a)	+9.1 (6.9)	+12.6 (7.4)	+7.7 (7.4)	+6.3 (7.0)	-2.8 (7.5)

S.E.M. = standard error of the least-square mean.
Not every subject had an end-of-treatment measurement for every variable; "n" sizes varied from 43 to 51.

C98-258:

Table 1
Mean Percent Changes (S.E.M.)[a] From Baseline to Study Endpoint in Plasma Concentrations of Various Lipid-Related Variables in the Intent-to-Treat Data Set

		SCH 58235			
Variables	Placebo (n=36)	mg AM (n=35)	mg PM (n=40)	10 mg AM (n=36)	10 mg PM (n=36)
Direct LDL-C	-4.9 (2.0)	-16.7 (1.9)	-13.8 (1.9)	-17.5 (1.9)	-18.2 (1.9)
Calculated LDL-C	-3.7 (1.9)	-16.7 (1.9)	-14.3 (1.8)	-18.1 (1.8)	-19.2 (1.8)
Apolipoprotein B	-4.7 (1.8)	-13.4 (1.8)	-12.0 (1.7)	-15.7 (1.8)	-15.1 (1.7)
HDL-C	-0.8 (1.9)	+4.1 (1.8)	+5.6 (1.7)	+2.4 (1.7)	+6.4 (1.8)
HDL_2-C	+10.3 (6.7)	+12.8 (6.7)	+16.1 (6.2)	+14.9 (6.7)	+18.4 (6.5)
HDL_3-C	-2.8 (2.9)	0 (2.9)	+3.5 (2.7)	-3.4 (2.9)	+4.8 (2.8)
Apolipoprotein A_1	-3.2 (2.1)	-1.2 (2.1)	+1.1 (2.0)	+0.6 (2.1)	+3.6 (2.0)
Total Cholesterol	-3.6 (1.4)	-12.5 (1.4)	-10.1 (1.3)	-13.6 (1.3)	-13.5 (1.3)
Triglycerides	-5.9 (4.9)	-11.3 (4.8)	-12.5 (4.6)	-12.6 (4.7)	-11.2 (4.7)
Lipoprotein(a)	+3.4 (8.9)	-4.5 (8.8)	+1.0 (8.4)	-1.1 (8.8)	+13.9 (8.5)

a: Least-square means and standard errors of the least-square means..
Not every subject had an end-of-treatment measurement for every variable; "n" sizes varied from 32 to 40.

Pravastatin Factorial Study:
Analysis of Pleiotropic Effects and Brachial Artery Reactivity of Coadministered Ezetimibe With Pravastatin in Patients With Primary Hypercholesterolemia:
In the pravastatin factorial study, median percent changes from baseline to endpoint in concentration of anti-inflammatory markers (CRP: C-reactive protein, ET-1: endothelin-1, TFP 1: Tissue Factor Pathway Inhibitor, TF: Tissue Factor, PAI-1: Plasminogen Activator Inhibitor-1) were compared between the treatment groups. Although no change in CRP, ET-1 and TFP 1 was noted in the placebo group, reductions of these markers were noted in the pooled pravastatin alone and pooled coadministration treatment

groups. Ezetimibe alone resulted in reduction in ET-1 and TFP 1 only. There was no effect on TF of these three groups compared to placebo. The administration of pravastatin alone resulted in a decrease in PAI-1 from baseline at endpoint, whereas there was an increase in the placebo group and greater increases in both the ezetimibe alone and pooled coadministration treatment groups, the latter 2 groups demonstrating similar increases. Fibrinogen decreased in the placebo group, was essentially unchanged from baseline in the ezetimibe alone group and increased in the pooled prava monotherapy and pooled coadministration treatment groups. It is not possible to draw any conclusions on the clinical relevance of these findings. However, for the pooled groups, the addition of ezetimibe to pravastatin did not seem to alter the ability of pravastatin to decrease CRP, ET-1 and TFP 1.
The analysis of brachial reactivity was not performed due to the enrollment of only 10 subjects.

B. Individual More Detailed Study Reviews (If performed)

MONOTHERAPY STUDIES P00474 and P00475:
Disposition of the subjects in P00474 and P00475:
76 (4%) subjects did not complete the double-blind treatment phase. Reasons for study discontinuation were:

	Placebo n= 431 (100%)	Ezetimibe n= 1288 (100%)
adverse event	11 (3%)	51 (4%)
treatment failure	0 (0%)	0 (0%)
lost to follow-up	3 (1%)	12 (1%)
subject did not wish to continue	12 (3%)	37 (3%)
noncompliance with protocol	3 (1%)	6 (<1%)
did not meet protocol eligibility	0 (0%)	0 (0%)
administrative	0 (0%)	2 (<1%)

Protocol Deviations in P00474 and P00475::
Protocol deviations were identified for 342 (20%) subjects. These deviations involved noncompliance with the protocol in 242 subjects (14%) and unacceptable concomitant therapy in 135 (8%). Other deviations included: did not meet entrance criteria- 26 (2%); insufficient washout- 14 (1%) and administrative 1 (<1%). These deviations were sufficient to result in exclusion from the Protocol-Evaluable Data Set for only 60 (3%) of these subjects. There was no pattern to suggest that there were more deviations or a difference in the types of deviations in either treatment group.

Data Sets Analyzed for Efficacy Evaluation:
Intent-to-Treat Data Set (ITT): all subjects who received randomized treatment assignment;
Protocol-Evaluable Data Set: all subjects in the ITT data set with the following exclusions:

-subjects on lipid-altering therapy for at least 2 weeks during the course of the study or at the time of the final blood draw if the subject discontinued prematurely;
-subjects with washout of lipid-altering therapy <30 days before the initial qualifying lipid determination;
-subjects with >10 kg weight change during the study;
-subjects with TSH >15 uU/ml during the study.
20 (5%) subjects in the placebo group and 57 subjects (4%) in the ezetimibe group were excluded from the Protocol-Evaluable Data Set primarily because of insufficient washout of lipid-altering agents or a >10 kg weight gain during the study.

The following table demonstrates why the sample size at week 12 and endpoint for studies P00474 and P00475 are not identical to baseline:

Status	Placebo (n= 431)	Ezetimibe (n= 1,288)
Week 12:		
Discontinuation before continuing to week 12	26	96
No lipid sample in week 12 window	10	25
LDL-C not determined from lipid sample in week 12 window	13	22
Endpoint:		
No lipid sample collected	4	14
LDL-C not determined from last lipid sample	18	40

Demographics and Other Baseline Characteristics in Studies P00474 and P00475:
In general, the two treatment groups were well balanced with regard to diet, weight, gender, age, race, physical activity and smoking history.
Approximately one-third of the subjects had a known family history of coronary artery disease and approximately one-third had some degree of hypertension. Other CV risk factors were much less frequent ($\leq$ 12% of subjects in either treatment group).

Measurements of Treatment Compliance and Other Factors That Could Affect Response:
Overall, the results showed good compliance with the dosing schedule, visit schedule, compliance with the diet and consistency in body weight and physical activity. There were no obvious differences among groups that could have affected the interpretation of the outcome.

Efficacy Analyses By Study- P00474 and P00475 and Combined: Lipid Parameters:
(Note: the following analyses for the lipid variables are presented for the ITT population only since the results for the Protocol-Evaluable Data Set were similar).

LDL-C:

P00474: Change in Plasma LDL-C (Direct and Calculated) Between Baseline and Endpoint (Intent-to-Treat Data Set):

	Direct LDL-C			Calculated LDL-C		
	Placebo	Ez	Ez Minus Placebo[a]	Placebo	Ez	Ez Minus Placebo[a]
Baseline: Mean(mg/dl) (n)	164.4 (n= 204)	165.2 (n= 621)		163.5 (n= 205)	164.4 (n= 622)	
Endpoint: Mean (mg/dl) (n)	164.9 (n= 199)	135.6 (n= 606)		165.1 (n= 201)	134.4 (n= 605)	
Mean % Δ from base	0.8	-17.7	-18.5 (-20.2, -16.7); p≤0.01	1.4	-18.2	-19.6 (-21.3, -17.9); p≤0.01

a= least-squares means and confidence interval

P00475: Change in Plasma LDL-C (Direct and Calculated) Between Baseline and Endpoint (Intent-to-Treat Data Set):

	Direct LDL-C			Calculated LDL-C		
	Placebo	Ez	Ez Minus Placebo[a]	Placebo	Ez	Ez Minus Placebo[a]
Baseline: Mean(mg/dl) (n)	168.0 (n= 226)	167.8 (n= 665)		167.5 (n= 226)	166.9 (n= 666)	
Endpoint: Mean (mg/dl) (n)	168.9 (n= 210)	138.6 (n= 628)		169.1 (n= 218)	136.8 (n= 657)	
Mean % Δ from base	0.4	-16.9	-17.2 (-18.9, -15.5) p≤0.01	1.1	-17.7	-18.8 (-20.4, -17.2) p≤0.01

a= least-squares means and confidence interval

P00474+ P00475: Change in Plasma LDL-C (Direct and Calculated) Between Baseline and Endpoint (Intent-to-Treat Data Set):

	Direct LDL-C			Calculated LDL-C		
	Placebo	Ez	Ez Minus Placebo[a]	Placebo	Ez	Ez Minus Placebo[a]
Baseline: Mean(mg/dl) (n)	166.3 (n= 430)	166.4 (n= 1,286)		165.4 (n= 431)	165.5 (n= 1,288)	
Endpoint: Mean (mg/dl) (n)	166.6 (n= 409)	137.0 (n= 1,234)		166.6 (n= 419)	135.0 (n= 1,262)	
Mean % Δ from base	0.3	-17.4	-17.7 (-19.0, -16.5); p≤0.01	0.9	-18.2	-19.1 (-20.3, -18.0); p≤0.01

a= least-squares means and confidence interval

Comments on the effects of placebo and ezetimibe on LDL-c:

The individual monotherapy studies demonstrated similar changes from baseline to endpoint in plasma LDL-c for the treatment groups (placebo and ez). Also, the results

obtained for direct LDL-C were similar to those obtained for calculated LDL-C. In the combined analysis, the mean % change in LDL-C from baseline to endpoint was <1 % in the placebo group while the eze group demonstrated a 17-18% reduction in LDL-C. This difference between the two treatment groups was significant ($p < 0.01$).

Key Secondary Variables:

Change in Plasma Total Cholesterol (TC) Between Baseline and Endpoint (Intent-to-Treat Data Set):

	Total Cholesterol					
	P00474		P00475		Combined	
	Placebo	Ez	Placebo	Ez	Placebo	Ez
Baseline: Mean (mg/dl) (n)	248.7 (n= 205)	249.1 (n= 622)	254.5 (n= 226)	252.8 (n= 666)	252.1 (n= 431)	251.3 (n= 1,288)
Endpoint: Mean (mg/dl) (n)	249.7 (n= 203)	218.0 (n= 615)	256.7 (n= 224)	220.7 (n= 659)	(n= 427)	(n= 1,274)
Mean % Δ from base	0.6	-12.4	0.8	-12.5	0.4	-12.7
Ez-Placebo: Least-squares means (CI)[a]	-13.0% (-14.2, -11.7) $p \leq 0.01$		-13.3% (-14.5, -12.1) $p \leq 0.01$		-13.1% (-14.0, -12.2) $p \leq 0.01$	

a= confidence interval

Comment on the effects of placebo and ezetimibe on TC:

In both the individual and combined studies, the mean % change in TC from baseline to endpoint was <1% for the placebo group while the ezetimibe group demonstrated a 12-13% reduction. The difference between ezetimibe and placebo in the individual studies and the combined analysis was significant ($p < 0.01$).

Change in Plasma Triglycerides (TG) Between Baseline and Endpoint (Intent-to-Treat Data Set):

(Note: the median baseline and endpoint and median % change from baseline were also calculated to account for the variability and skewness commonly observed with TG levels):

	Triglycerides					
	P00474		P00475		Combined	
	Placebo	Ez	Placebo	Ez	Placebo	Ez
Baseline: (n)	(n= 205)	(n= 622)	(n= 226)	(n= 666)	(n= 431)	(n= 1,288)
Median (mg/dl)	162.7	158.7	163.7	161.7	163.7	160.5
Mean (mg/dl)	171.2	163.0	174.8	169.0	174.9	167.7
Endpoint: (n)	(n= 203)	(n= 615)	(n= 224)	(n= 659)	(n= 427)	(n= 1,274)
Median % Δ from base	-1.2	-7.3	2.2	-9.3	0.0	-8.0
Mean % Δ from base	2.4	-1.7	5.7	-5.7	3.6	-4.2
Ez-Placebo: Least-squares means (CI)[a]	-4.1% (-8.9, 0.6), p= 0.09		-11.4% (-15.5, -7.3) $p \leq 0.01$		-7.8% (-10.9, -4.7) $p \leq 0.01$	

a= confidence interval

Comment on the effects of placebo and ezetimibe on TG:

In study P00474 there was not a statistically significant difference between ezetimibe and placebo in the median % change from baseline to endpoint in TG levels. However, the difference between the two treatment groups was significant for study P00475 and for the

combined analysis. The sponsor attributed the inconsistency between the two monotherapy studies to the high variability commonly observed for this parameter.

Change in Plasma HDL-C Between Baseline and Endpoint (Intent-to-Treat Data Set):

	HDL-C					
	P00474		P00475		Combined	
	Placebo	Ez	Placebo	Ez	Placebo	Ez
Baseline: Mean (mg/dl) (n)	51.0 (n= 205)	52.1 (n= 622)	52.2 (n= 226)	52.1 (n= 666)	51.7 (n= 431)	52.3 (n= 1,288)
Endpoint: Mean % Δ from base (n)	-1.3 (n= 203)	1.0 (n= 615)	-1.6 (n= 224)	1.3 (n= 659)	-1.6 (n= 427)	1.0 (n= 1,274)
Ez-Placebo: Least-squares means (CI)[a]	2.3% (0.6, 3.9) $p \leq 0.05$		2.9% (1.4, 4.4) $p \leq 0.01$		2.6% (1.5, 3.7) $p \leq 0.01$	

a= confidence interval

Comment on the effects of placebo and ezetimibe on HDL-C:

In both the individual and combined studies, the mean % change in HDL-C from baseline to endpoint was -1 to -2% for the placebo group while the ezetimibe group demonstrated a 1% increase. The difference between ezetimibe and placebo in the individual studies and the combined analysis was significant.

(Note: the reduction in LDL-C, TC, TG and HDL-C by ezetimibe occurred as early week 2).

Change in Apolipoprotein B (Apo B) Between Baseline and Endpoint (Intent-to-Treat Data Set):

	Apo B					
	P00474		P00475		Combined	
	Placebo	Ez	Placebo	Ez	Placebo	Ez
Baseline: Mean (mg/dl) (n)	160.6 (n= 205)	161.6 (n= 620)	164.4 (n= 225)	164.2 (n= 662)	163.4 (n= 430)	163.6 (n= 1,282)
Endpoint: Mean % Δ from base (n)	-1.0 (n= 200)	-15.4 (n= 598)	-1.4 (n= 217)	-15.5 (n= 637)	-1.6 (n= 417)	-15.7 (n= 1,235)
Ez-Placebo: Least-squares means (CI)[a]	-14.4% (-16.1, -12.6) $p \leq 0.01$		-14.1% (-15.8, -12.5) $p \leq 0.01$		-14.1% (-15.3, -12.9) $p \leq 0.01$	

a= confidence interval

Comment on the effects of placebo and ezetimibe on Apo B:

In both the individual and combined studies, the mean % change in Apo B from baseline to endpoint was –1 to -2% for the placebo group while the ezetimibe group demonstrated a 15-16% reduction. This result is consistent with the effect of ezetimibe in decreasing circulating LDL-C. The difference between ezetimibe and placebo in the individual studies and the combined analysis was significant.

Change in Lp(a) Between Baseline and Endpoint (Intent-to-Treat Data Set):
(Note: the median baseline and endpoint and median % change from baseline were also calculated to account for the variability commonly observed with Lp(a) levels):

	Lp(a)					
	P00474		P00475		Combined	
	Placebo	Ez	Placebo	Ez	Placebo	Ez
Baseline:						
(n)	(n= 205)	(n= 618)	(n= 225)	(n= 661)	(n= 430)	(n= 1,279)
Median (mg/dl)	20	21	17	22	18	22
Mean (mg/dl)	33.6	30.8	27.5	33.5	30.4	32.3
Endpoint:						
(n)	(n= 200)	(n= 593)	(n= 215)	(n= 633)	(n= 415)	(n= 1,226)
Median % Δ from base	-3.7	-9.4	-1.8	-5.6	-3.0	-7.7
Mean % Δ from base	1.8	-7.5	16.3	2.8	7.5	-3.7
Ez-Placebo: Least-squares means (CI)[a]	-9.3% (-15.4, -3.1) $p \leq 0.01$		-13.5% (-25.0, -2.0) $p \leq 0.05$		-11.1% (-17.8, -4.4) $p \leq 0.01$	

a= confidence interval

Comment on the effects of placebo and ezetimibe on Lp(a):
Note the wide variability in response between the two monotherapy studies for each treatment group. This was attributed to the wide variability commonly observed in levels for this parameter. Nevertheless, the difference between ezetimibe and placebo in both the individual studies and the combined analysis was significant.

Mean % Change From Baseline to Endpoint in HDL_2-C, HDL_3-C, Apo A-1, the ratios: direct LDL-C/HDL-C and TC/HDL-C and Lp(a): Studies P00474 and P00475 (note: the sample size stated is that at baseline; and Ez-Placebo is the least-squares means and confidence interval based on the ANOVA model; NS= not significant):

	Rx. Gp.	HDL_2-C	HDL_3-C	Apo A-1	dir LDL/ HDL	TC/HDL	Lp(a)
P00474	Placebo	-1.1% (n= 200)	3.9% (n= 200)	1.2% (n= 205)	2.3% (n= 204)	2.1% (n= 205)	1.8% (n= 205)
	Ez	5.0% (n= 614)	2.8% (n= 614)	2.3% (n= 620)	-18.3% (n= 621)	-12.8% (n= 622)	-7.5% (n= 618)
	Ez-Plac	6.2% (1.4, 11.0) $p \leq 0.05$	-1.1% (-4.2, 2.1) NS	1.1% (-0.8, 2.9) NS	-20.5% (-22.6, -18.5), $p \leq 0.01$	-14.9% (-16.6, -13.2), $p \leq 0.01$	-9.3% (-15.4, -3.1), $p \leq 0.01$
P00475	Placebo	0.6% (n= 218)	1.0% (n= 218)	1.9% (n= 225)	2.7% (n= 226)	3.0% (n= 226)	16.3% (n= 225)
	Ez	1.3% (n= 652)	5.7% (n= 652)	2.5% (n= 662)	-17.5% (n= 665)	-13.1% (n= 666)	2.8% (n= 661)
	Ez-Plac	0.7% (-3.7, 5.1) NS	4.6% (1.8, 7.4) $p \leq 0.01$	0.6% (-1.2, 2.4) NS	-20.1% (-22.1, -18.2), $p \leq 0.01$	-16.1% (-17.7, -14.5), $p \leq 0.01$	-13.5% (-25.0, -2.0), $p \leq 0.05$
474+475	Placebo	-1.5% (n= 418)	2.4% (n= 418)	1.2% (n= 430)	2.4% (n= 430)	2.4% (n= 431)	7.5% (n= 430)
	Ez	1.4% (n= 1,266)	4.4% (n= 1,266)	2.0% (n= 1,282)	-17.8% (n= 1,286)	-13.1% (n= 1,288)	-3.7 (n= 1,279)
	Ez-Plac	2.9% (-0.4, 6.2) NS	2.0% (-0.1, 4.1) NS	0.8% (-0.6, 2.0) NS	-20.2% (-21.6, -18.8), $p \leq 0.01$	-15.5% (-16.7, -14.3), $p \leq 0.01$	-11.1 (-17.8, -4.4), $p \leq 0.01$

Comment on the above table:
For the combined analysis, the difference between ezetimibe and placebo was not significant for the HDL-C subfractions or for Apo A-1 but was for Lp(a) and for the ratios of direct LDL-C/HDL-C and for TC/HDL-C.

FACTORIAL CO-ADMINISTRATION STUDIES: P00679, 680, 691 and 692: Efficacy Analyses By Study- Lipid Parameters:
(Note: the following analyses for the lipid variables are presented for the ITT population only since the results for the Protocol-Evaluable Data Set were not meaningfully different)

Direct LDL-C: Mean % Change From Baseline to Endpoint Pooled Across All Doses of a Given Statin: Factorial Coadministration Studies:

Mean Percent Change in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Factorial Coadministration Studies (Intent-to-Treat Data Set)					
	Ez	Statin (all doses)	Ez +Statin (all doses)	[Ez + Statin] – [Ez][a] (95% CI)	[Ez + Statin] – [Statin][b] (95% CI)
Lovastatin	-18.6 (n= 72)	-24.7 (n= 220)	-39.0 (n= 192)	-20.4 (-24.2, -16.7), $p \leq 0.01$	-14.3 (-17.0, -11.6), $p \leq 0.01$
Simvastatin	-18.1 (n= 61)	-36.1 (n= 263)	-49.9 (n= 273)	-31.8 (-35.9, -27.8), $p \leq 0.01$	-13.8 (-16.3, -11.4), $p \leq 0.01$
Pravastatin	-18.7 (n= 64)	-24.3 (n= 205)	-37.7 (n= 204)	-19.0 (-22.5, -15.5), $p \leq 0.01$	-13.4 (-15.8, -11.0), $p \leq 0.01$
Atorvastatin	-18.4 (n= 65)	-42.4 (n= 248)	-54.5 (n= 255)	-36.1 (-40.2, -32.0), $p \leq 0.01$	-12.1 (-14.7, -9.5), $p \leq 0.01$

a= difference between pooled doses of a given statin coadministered with ezetimibe versus ezetimibe alone

b= difference between pooled doses of a given statin coadministered with ezetimibe versus pooled doses of a given statin alone

Direct LDL-C: Individual Treatment Groups:

Mean Percent Change in Direct LDL-C Between Baseline and Endpoint: Factorial Coadministration Studies: By Statin, By Dose (Intent-to-Treat Data Set)										
	Plac	Ez	Statin 10 mg	Ez + Statin 10 mg	Statin 20 mg	Ez + Statin 20 mg	Statin 40 mg	Ez + Statin 40 mg	Statin 80 mg	Ez + Statin 80 mg
Lovastatin:	N= 64[a]	N= 72[a]	N= 73[a]	N= 65[a]	N= 74[a]	N= 62[a]	N= 73[a]	N= 65[a]	-	-
Mean % Δ	-0.3	-18.6	-19.0	-33.1	-26.0	-39.4	-29.2	-44.5	-	-
Diff. in mean % Δ (95% CI)		-18.6 (-23.3, -13.9), $p \leq 0.01$[b]		-14.2 (-18.8, -9.5), $p \leq 0.01$[c]		-13.5 (-18.2, -8.8), $p \leq 0.01$[c]		-15.3 (-20.0, -10.7), $p \leq 0.01$[c]		
Simvastatin:	N= 70	N= 61	N= 70	N= 67	N= 61	N= 69	N= 65	N= 73	N= 67	N= 64
Mean % Δ	-1.3	-18.1	-27.4	-44.4	-36.3	-44.8	-36.3	-53.5	-44.3	-56.8
Diff. in mean % Δ (95% CI)		-16.7 (-21.7, -11.7), $p \leq 0.01$[b]		-17.0 (-21.8, -12.2), $p \leq 0.01$[c]		-8.5 (-13.5, -3.5), $p \leq 0.01$[c]		-17.2 (-22.0, -12.3), $p \leq 0.01$[c]		-12.6 (-17.6, -7.6), $p \leq 0.01$[c]
Pravastatin:	N= 65	N= 64	N= 66	N= 71	N= 69	N= 66	N= 70	N= 67	-	-
Mean % Δ	+1.3	-18.7	-19.7	-34.1	-23.8	-38.0	-29.4	-41.1	-	-
Diff. in mean % Δ (95% CI)		-20.1 (-24.4, -15.7), $p \leq 0.01$[b]		-14.4 (-18.6, -10.2), $p \leq 0.01$[c]		-14.2 (-18.4, -10.0), $p \leq 0.01$[c]		-11.7 (-15.9, -7.5), $p \leq 0.01$[c]		
Atorvastatin:	N= 60	N= 65	N= 60	N= 65	N= 60	N= 62	N= 66	N= 65	N= 62	N= 63
Mean % Δ	+5.9	-18.4	-35.5	-50.4	-39.8	-53.7	-43.1	-54.3	-51.4	-59.7
Diff. in mean % Δ (95% CI)		-24.3 (-29.6, -19.1), $p \leq 0.01$[b]		-14.9 (-20.2, -9.7), $p \leq 0.01$[c]		-13.9 (-19.2, -8.6), $p \leq 0.01$[c]		-11.3 (-16.5, -6.1), $p \leq 0.01$[c]		-8.3 (-13.6, -3.1), $p \leq 0.01$[c]

a= sample size at baseline

b= pairwise comparison of ezetimibe versus placebo

c= pairwise comparison of ez + statin to the same dose of statin

Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Direct LDL-C[a] (ITT):

Lovastatin:

	[Ezetimibe + Placebo] – [Placebo]	[Ezetimibe 10 mg] – [Lova 10 mg]
Diff. in mean % Δ from baseline to endpoint for direct LDL-C (95% CI) (p value)	-18.6 (-23.3, -13.9), p < 0.01	0.4 (-4.2, 4.9), not significant: p=0.88

	Ez+ Lova 10mg	Ez+ Lova 20mg	Ez+ Lova 40mg
Diff. from same dose of lova alone in mean % Δ from base (95% CI) (p value)	-14.20 (-18.8, -9.5) p < 0.01	-13.5 (-18.2, -8.8) p < 0.01	-15.3 (-20.0, -10.7) p < 0.01
Diff, from next higher dose of lova alone in mean % Δ from base (95% CI)(p value	-7.2 (-11.8, -2.5) p < 0.01	-10.3 (-15.0, -5.6) p < 0.01	Not applicable
Diff. from second higher dose of lova alone in mean % Δ from base(95%CI)(p)	-4.0 (-8.6, +0.7) not significant: p= 0.10	Not applicable	Not applicable

Simvastatin: Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Direct LDL-C[a] (ITT):

	[Ezetimibe + Placebo] – [Placebo]	[Ezetimibe 10 mg] – [Simva 10 mg]
Diff. in mean % Δ from baseline to endpoint for direct LDL-C (95% CI) (p value)	-16.7 (-21.7, -11.7), p < 0.01	Not performed

	Ez +Simva10mg	Ez +Simva20mg	Ez +Simva40mg	Ez +Simva80mg
Diff. from same dose of simva alone in mean % Δ from base (95% CI) (p value)	-17.0 (-21.8, -12.2), p < 0.01	-8.5 (-13.5, -3.5), p < 0.01	-17.2 (-22.0, -12.3), p < 0.01	-12.6 (-17.6, -7.6), p < 0.01
Diff, from next higher dose of simva alone in mean % Δ from base (95% CI) (p value)	-8.1 (-13.1, -3.2), p < 0.01	-8.5 (-13.4, -3.6), p < 0.01	-9.2 (-14.0, -4.4), p < 0.01	Not applicable
Diff. from second higher dose of simva alone in mean % Δ from base(95%CI) (p value)	-8.1 (-13.1, -3.2), p < 0.01	-0.5 (-5.4, 4.3) not significant: p = 0.83	Not applicable	Not applicable
Diff. from highest dose of simva alone in mean % Δ from base(95%CI) (p value)	-0.1, p= 0.94	Not applicable	Not applicable	Not applicable

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Pravastatin: Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Direct LDL-C[a] (ITT):

	[Ezetimibe + Placebo] – [Placebo]	[Ezetimibe 10 mg] – [Prava 10 mg]
Diff. in mean % Δ from baseline to endpoint for direct LDL-C (95% CI) (p value)	-20.1 (-24.4, -15.7), p < 0.01	1.0 (-3.3, 5.3), not significant: p=0.7

	Ez+ Prava 10mg	Ez+ Prava 20mg	Ez+ Prava 40mg
Diff. from same dose of prava alone in mean % Δ from base (95% CI) (p value)	-14.4 (-18.6, -10.2) p < 0.01	-14.2 (-18.4, -10.0) p < 0.01	-11.7 (-15.9, -7.5) p < 0.01
Diff, from next higher dose of prava alone in mean % Δ from base (95% CI)(p	-10.3 (-14.5, -6.2) p < 0.01	-8.5 (-12.8, -4.3) p < 0.01	Not applicable
Diff. from second higher dose of prava alone in mean % Δ from base(95%CI)(p)	-4.7 (-8.8, -0.5): p = 0.03	Not applicable	Not applicable

Atorvastatin: Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Direct LDL-C[a] (ITT):

	[Ezetimibe + Placebo] – [Placebo]	[Ezetimibe 10 mg] – [Atorva 10 mg]
Diff. in mean % Δ from baseline to endpoint for direct LDL-C (95% CI) (p value)	-24.3 (-29.6, -19.1), p < 0.01	Not performed

	Ez +Atorv10mg	Ez +Atorv20mg	Ez +Atorv40mg	Ez +Atorv80mg
Diff. from same dose of atorva alone in mean % Δ from base (95% CI) (p value)	-14.9 (-20.2, -9.7), p < 0.01	-13.9 (-19.2, -8.6), p < 0.01	-11.3 (-16.5, -6.1), p < 0.01	-8.3 (-13.6, -3.1), p < 0.01
Diff, from next higher dose of atorva alone in mean % Δ from base (95% CI) (p value)	-10.6 (-15.8, -5.4), p < 0.01	-10.7 (-15.9, -5.4), p < 0.01	-3.0 (-8.2, 2.3), not significant: p = 0.26	Not applicable
Diff. from second higher dose of atorva alone in mean % Δ from base(95%CI) (p value)	-7.3 (-12.5, -2.2), p < 0.01	-2.4 (-7.6, 2.9) not significant: p = 0.38	Not applicable	Not applicable
Diff. from highest dose of atorva alone in mean % Δ from base(95%CI) (p value)	+1.0, p= 0.71	Not applicable	Not applicable	Not applicable

Comment on above tables:

Coadministration of ezetimibe with the lowest dose of statin, 10 mg, resulted in LDL-C concentrations similar to than that seen with the highest dose tested of statin alone.

The following table and figures demonstrate that the LDL-C lowering effects for all active treatments were seen as early as week 2 and were maintained for the 12-week duration period of these studies:

Change in Plasma Concentration of Calculated LDL-C Between baseline and Endpoint: Factorial Coadministration Studies: Pooled Across All Statins (Intent-to-Treat data Set)					
	Placebo[a]	Ez 10 mg[a]	All Statin[b]	Ez +All Statin[b]	[Pooled Ez + Statin] – [Pooled Statin] (95% CI)
Mean baseline in mg/dl (SEM)	(n= 259) 179.3 (1.3)	(n= 262) 179.6 (1.3)	(n= 936) 179.5 (0.7)	(n= 925) 178.5 (0.7)	
Week 2: Mean % Δ from baseline (SEM)	(n= 247) -0.1 (0.6)	(n= 248) -19.5 (0.6)	(n= 901) -32.5 (0.4)	(n= 886) -48.9 (0.4)	-16.4 (-17.5, -15.3)
Week 4: Mean % Δ from baseline (SEM)	(n= 244) -0.3 (0.7)	(n= 253) -20.4 (0.6)	(n= 906) -35.1 (0.4)	(n= 889) -49.8 (0.4)	-14.7 (-15.9, -13.5)
Week 8: Mean % Δ from baseline (SEM)	(n= 237) -0.2 (0.7)	(n= 244) -20.6 (0.7)	(n= 875) -34.5 (0.5)	(n= 857) -49.2 (0.5)	-14.7 (-15.9, -13.4)
Week 12: Mean % Δ from baseline (SEM)	(n= 220) 1.3 (0.8)	(n= 225) -19.7 (0.7)	(n= 835) -34.0 (0.5)	(n= 817) -48.1 (0.5)	-14.1 (-15.4, -12.7)
Endpoint: Mean % Δ from baseline (SEM)	(n= 255) 0.6 (0.8)	(n= 259) -19.3 (0.7)	(n= 928) -32.8 (0.5)	(n= 917) -46.6 (0.5)	-13.8 (-15.2, -12.4)
a: means and standard errors are sample mean and sample standard errors b: means and standard errors are least-square means and standard errors based on the ANOVA model All Statin= pool of all doses of statin; Ez + All Statin= pool of all doses of statin coadministered with Ez					

(Note: similar results were obtained for direct LDL-C).

P00679:

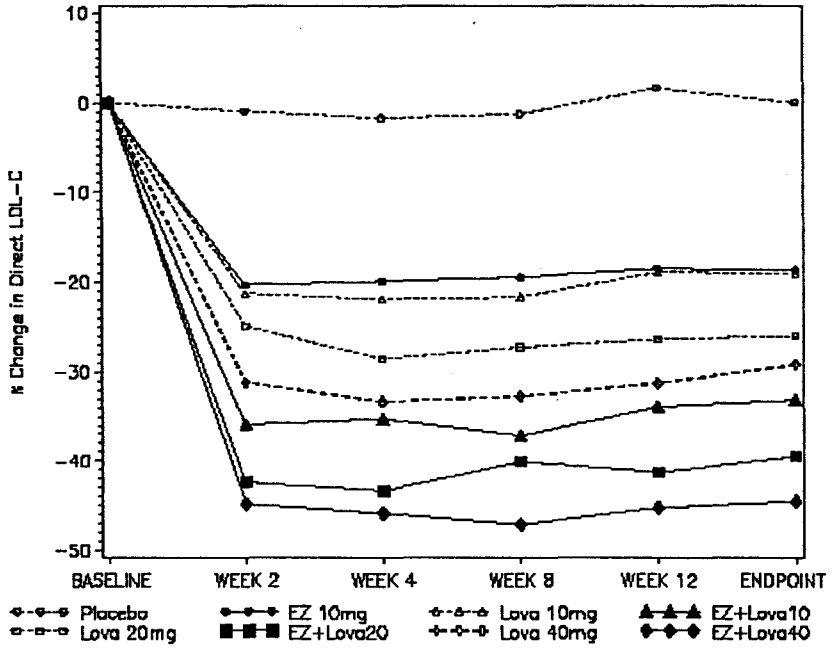

Figure 3 Mean percent change from baseline in plasma concentration of direct LDL-C over time and at endpoint for the individual treatment groups: Intent-to-Treat Data Set.
Source Data: **Section 14.2.2.1.1.1.**

P00680:

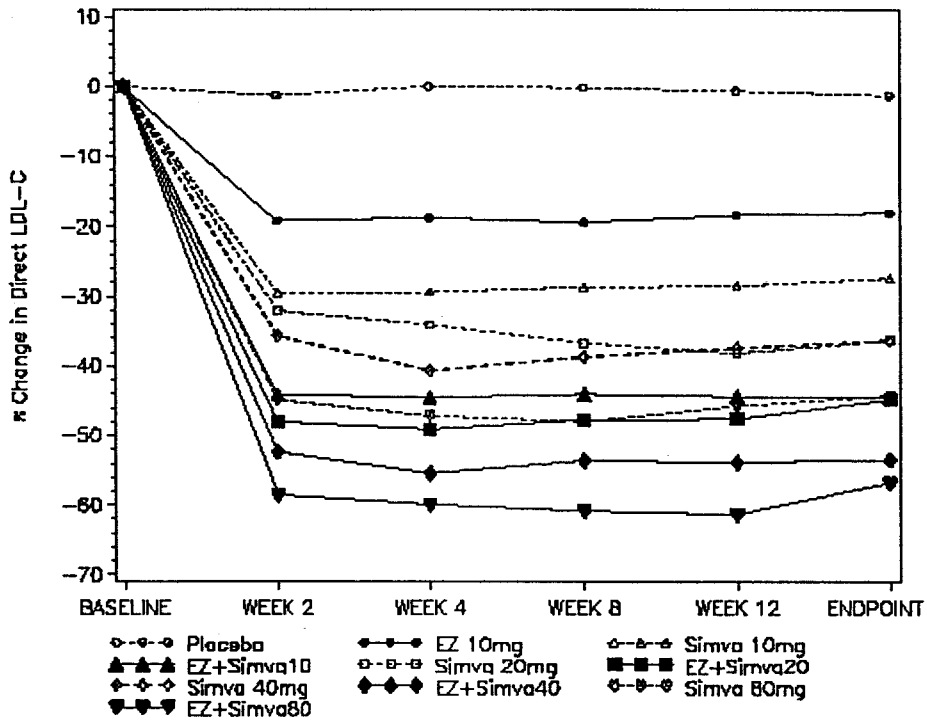

Figure 3 Mean percent change from baseline in plasma concentration of direct LDL-C over time and at endpoint: Intent-to-Treat Data Set (Individual Treatment Groups).
Source Data: **Section 14.2.2.1.1.1.**

P00691:

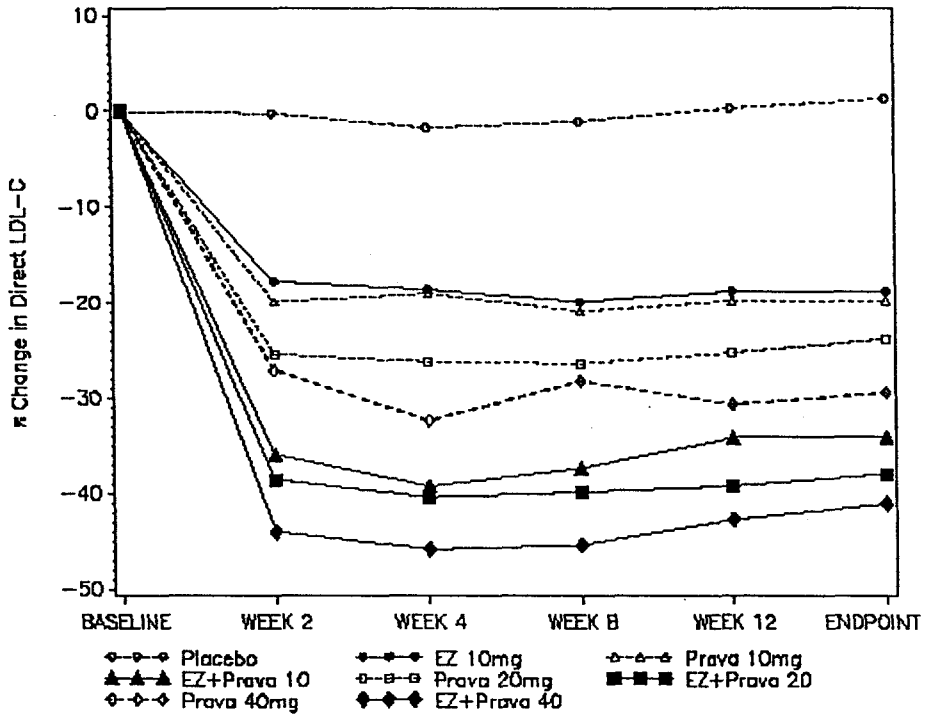

Figure 3 Mean percent change from baseline in plasma concentration of direct LDL-C over time and at endpoint for the individual treatment groups: Intent-to-Treat Data Set.

Source Data: Section 14.2.2.1.1.1.

P00692:

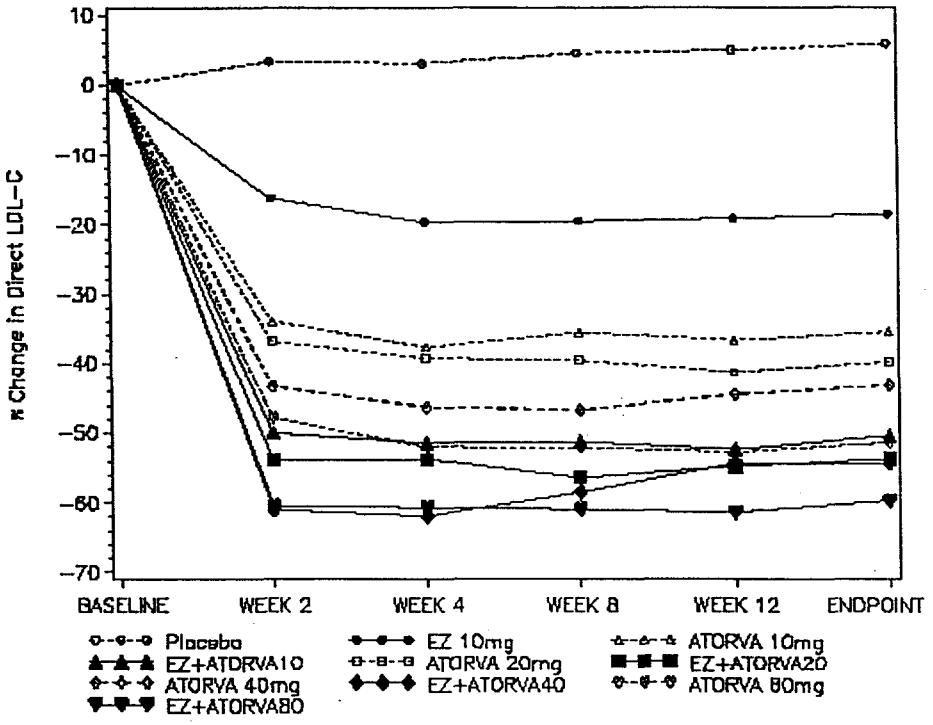

Figure 3 Mean percent change from baseline in plasma concentration of direct LDL-C over time and at endpoint for the individual treatment groups: Intent-to-Treat Data Set.
Source Data: **Section 14.2.2.1.1.1.**

ADD-ON STUDY: P02173:

Demographics and Other Baseline Characteristics:
The data set consisted of 326 females and 443 males, ages 22 to 85 years old with baseline plasma concentrations of calculated LDL-C ranging from 71-455 mg/dl. Mean baseline LDL-C levels were comparable between the statin + placebo and statin + ezetimibe treatment groups, being 138.8 and 138.1 mg/dl, respectively. This was true for other lipid and for lipoprotein variables. In general, the treatment groups were also balanced with regard to age, gender, race, diet, weight and BMI.

Number (%) of Subjects With the Indicated Baseline CV Risk factor Categories and Stratum: ITT Data Set:

Risk Factor	Stratum	Statin + Placebo (n= 390)	Statin + Ezetimibe (n= 379)
No CHD, <2 risk factors LDL-C ≥ 160 mg/dl	I	19 (56)	19 (48)
	II	15 (44)	21 (53)
No CHD, ≥2 risk factors LDL-C ≥ 130 mg/dl	I	36 (45)	55 (59)
	II	44 (55)	39 (41)
CHD and/or DM, LDL-C ≥ 100 mg/dl	I	135 (49)	125 (51)
	II	141 (51)	120 (49)
Stratum I: LDL-C <18% above the NCEP-defined target; Stratum II: LDL-C ≥18% above the target			

9.6% (74/769) of subjects had no CHD and <2 CV risk factors with LDL-C ≥160 mg/dl; 22.6% (174/769) of subjects had no CHD and ≥2 CV risk factors with LDL ≥130 mg/dl; 67.7% (521/769) of subjects had CHD and/or CHD-equivalent disease with LDL ≥ 100 mg/dl.

The number (%) of subjects by baseline statin therapy: ITT Data Set:

Statin Type	Statin + Placebo (n= 390)	Statin + Ezetimibe (n= 379)
Simvastatin	117 (30.0)	123 (32.5)
Atorvastatin	162 (41.5)	146 (38.5)
Lovastatin	12 (3.1)	7 (1.8)
Pravastatin	55 (14.1)	55 (14.5)
Fluvastatin	19 (4.9)	30 (7.9)
Cerivastatin	25 (6.4)	18 (4.7)

The two treatment groups were balanced with regard to statin type. ~1/3 of the subjects were receiving simvastatin; ~40%, atorvastatin and, the remainder, other statins (lovastatin, pravastatin, fluvastatin or cerivastatin).

Number (%) of Subjects by Baseline Dose of Statin:

Statin Type	Dose (mg)	Statin + Placebo	Statin + Ezetimibe
Simvastatin	5 mg	1 (0.3)	3 (0.8)
	10 mg	8 (2.1)	12 (3.2)
	20 mg	41 (10.5)	43 (11.3)
	30 mg	3 (0.8)	3 (0.8)
	40 mg	40 (10.3)	41 (10.8)
	50 mg	0	1 (0.3)
	60 mg	1 (0.3)	2 (0.5)
	80 mg	23 (5.9)	18 (4.7)
Atorvastatin	—	1 (0.3)	1 (0.3)
	10 mg	46 (11.8)	38 (10.0)
	20 mg	41 (10.5)	42 (11.1)
	30 mg	4 (1.0)	4 (1.1)
	40 mg	35 (9.0)	28 (7.4)
	50 mg	1 (0.3)	0
	60 mg	3 (0.8)	5 (1.3)
	70 mg	1 (0.3)	0
	80 mg	30 (7.7)	28 (7.4)
Lovastatin	10 mg	4 (1.0)	0
	20 mg	4 (1.0)	4 (1.1)
	30 mg	1 (0.3)	0
	40 mg	2 (0.5)	3 (0.8)
	60 mg	1 (0.3)	0
Pravastatin	—	1 (0.3)	0
	10 mg	4 (1.0)	8 (2.1)
	20 mg	27 (6.9)	18 (4.7)
	30 mg	0	1 (0.3)
	40 mg	20 (5.1)	26 (6.9)
	60 mg	3 (0.8)	0
	80 mg	0	2 (0.5)
Fluvastatin	20 mg	7 (1.8)	12 (3.2)
	40 mg	10 (2.6)	17 (4.5)
	80 mg	2 (0.5)	1 (0.3)
Cerivastatin	0.2 mg	6 (1.5)	1 (0.3)
	0.3 mg	3 (0.8)	4 (1.1)
	0.4 mg	15 (3.8)	8 (2.1)
	0.6 mg	0	1 (0.3)
	0.8 mg	1 (0.3)	4 (1.1)

The two treatment groups were balanced with regard to statin dose. Most subjects on simvastatin were receiving doses of 20, 40 or 80 mg. Most subjects receiving atorvastatin were receiving 10, 20, 40 or 80 mg.

>99% of subjects in both treatment groups showed compliance with the diet.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HoFH): STUDY P01030:

Title: A Phase III Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia (HoFH)

Background:

Current therapeutic options include high doses of HMG-CoA reductase inhibitors, LDL apheresis, portacaval shunting, and ultimately liver transplantation.
All subjects who completed the 12-week, double-blind treatment phase in the present study were eligible to continue treatment in an open-label 24 month study, P01417 that is still ongoing: Subjects received ezetimibe 10 mg coadministered with atorvastatin or simvastatin (each statin dosed and titrated as needed to 40-80 mg).

Baseline Demographics:
Overall, the baseline characteristics of the statin 80 mg treatment groups and the ez + statin 40/80 mg treatment groups were balanced for demographic characteristics.

Age, Sex and Race:

	Statin 80 mg (n= 17)	Ez + Statin 40/80 mg (n= 33)
Age: number (%):		
<18 years	2 (12%)	5 (15%)
≥18 years	15 (88%)	28 (85%)
Sex: number (%):		
Female	12 (71%)	17 (52%)
Male	5 (29%)	16 (48%)
Race: number (%):		
Caucasian	16 (94%)	29 (88%)
Black	0	1 (3%)
American Indian	0	0
Asian	0	0
Hispanic	1 (6%)	3 (9%)
Pacific Islander	0	0

Lipid Variables:
Note, that for the primary comparison, mean ± S.D. for baseline direct LDL-C was 345.9 mg/dl ± 85.2 for the statin 80 mg pooled treatment group versus 321 mg/dl ± 125.8 for the ez + statin 40/80 mg pooled treatment group. Based on the large standard deviations, the means for these pooled treatment groups were considered to be similar at baseline. For the individual statin alone treatment subgroups, the mean baseline direct LDL-C ranged from 326.9-353.8 mg/dl and for the ez + statin 40/80 mg subgroups, from 267.7-381.6 mg/dl. The corresponding levels for calculated LDL-C are depicted below:

Baseline calculated LDL-c levels (mg/dl): Intent-to-Treat Data Set:								
	Statin 80mg N= 17	Eze + Statin 40/80 mg N=33	Atorva 80 mg N= 12	Eze + Atorva 40 mg N= 12	Eze + Atorva 80 mg N= 12	Simva 80 mg N= 5	Eze + Simva 40 mg N= 4	Exe + Simva 80 mg N= 5
Mean	348.5	324	358	384.7	284.4	325.7	327.3	270.8
Median	308.3	308	343.7	393.5	288.7	297	313.3	282.7
Min-max								

Estimated LDL-Receptor Residual Activity

Distribution of Homozygous Subjects Across Treatment Groups by Estimated LDL-Receptor Residual Activity : Intent-to-Treat Data Set:								
Estimate LDL-Receptor Residual Activity	Statin 80 mg N= 17	Eze + Statin 40/80 mg N= 33	Atorva N= 12	Eze + Atorva 40 mg N= 12	Eze + Atorva 80 mg N= 12	Simva 80 mg N= 5	Eze + Simva 40 mg N= 4	Exe + Simva 80 mg N= 5
<5%	4	4	4	2	1	0	1	0
≥5%	2	6	2	2	4	0	0	0

Previous Treatment[a]:

Treatment	Statin 80 mg (n= 17)	Ez + Statin 40/80 mg (n= 33)
Lipid lowering medications[b]		
Atrorvastatin	12 (71%)	20 (61%)
Simvastatin	6 (35%)	4 (12%)
Cerivastatin	1 (6%)	0
Nicotinic acid	1 (6%)	1 (3%)
Fibrate	0	1 (3%)
Bile acid resin	2 (12%)	6 (18%)
Other	1 (6%)	0
Procedures[c]		
Operation on vessels	3 (18%)	4 (12%)
Operation on heart	3 (18%)	16 (48%)
Apheresis/Plasmapheresis	8 (47%)	19 (58%)

a= treatments received before, but not on or continuing after the date of visit 1 (week -14 to -6) were considered previous treatment

b= includes lipid lowering medications the subjects received within the past 2 years

c= includes any treatment related to FHH at any time during the subject's life prior to randomization

Comment on above table:

Only 1 subject required wash-out of fibrates as specified in the protocol. This subject was subsequently randomized to the ezetimibe + atorva 80 mg treatment group.

Concomitant Therapy[a]:

Treatment	Statin 80 mg (n= 17)	Ez + Statin 40/80 mg (n= 33)
Lipid lowering medications:		
Atorvastatin[b]	3 (18%)	9 (27%)
Simvastatin[b]	2 (12%)	0
Nicotinic acid	1 (6%)	0
Colestipol	0	1 (3%)
Questran	0	1 (3%)
Apheresis/Plasmapheresis[c]	8 (47%)	17 (52%)

a= treatments received on or after the date of visit 1 (week -14 to -6) were considered concomitant treatment

b= although 14 subjects continued previous statin treatment during the study, all subjects received their last dose of previous statin prior to or on the date of the first dose of open-label statin for the Statin Run-in phase

c= subjects on regular LDL apheresis prior to study entry were allowed to continue on that regimen during the study, provided that the interval between apheresis sessions was kept stable throughout the study. In these subjects, blood samples were collected for

lipid/lipoprotein analyses immediately prior to their weekly/bi-monthly apheresis session, when LDL-C values were at their highest.

Compliance with the Diet:
Generally, RISCC scores during treatment were within a range indicative of the NCEP Step 1 diet (14-20). The % of patients with RISCC scores 13-20 at week 12 were 85% for the pooled statin monotherapy groups and 57% for the pooled ezetimibe plus statin coadministration group. At study week 12, only 1 patient in the ez + statin group failed to comply with the diet (RISCC score $\geq$ 24) and none failed to comply in the statin alone group. The % of patients with RISCC scores <13, which is indicative of the NCEP Step II diet, was similar between the statin and eze+statin groups at baseline and week 2 but was higher in the ez + statin group at weeks 8 (36% vs. 15%, respectively) and 12 (33% vs. 8%, respectively).

HOMOZYGOUS SITOSTEROLEMIA: P02243 AND P02257:
Background:
Current treatment of homozygous sitosterolemia consists of dietary restriction of plant and shellfish sterols, as well as the use of bile salt binding resins. Ileal bypass surgery, to induce bile salt malabsorption, is another treatment option, particularly in patients who do not tolerate resin therapy.

The published literature was reviewed to assess the efficacy of resin therapy in these patients (the following references were submitted by the sponsor on August 9, 2001):

1. Belamarich (ref. 1): After 0.2 years (2.4 months) of a low sterol diet plus cholestyramine (8 g/day) therapy in an 11 year old boy with sitosterolemia, plasma cholesterol decreased by 58%; plasma sitosterol concentration by 42% and campesterol by 52% compared to baseline (unrestricted diet). During ~9 months of treatment, the patient had complete regression of all tuberous xanthomata. When measured 4 and 8 months following introduction of cholestyramine, his achilles tendon xanthomata regressed in breadth from 2.2 cm to 1.8 cm.
2. Cobb (ref. 7): treatment of a 10 year old girl with low sterol diet and cholestyramine 9 g/day x 3 weeks for homozygous sitosterolemia, produced dramatic reductions in plasma sterol, compared with diet-placebo, decreasing plasma sitostetrol, cholesterol and LDL-sterol proportionately by 29%, 31% and 41%, respectively.
3. Hidaka (ref. 11) treated 2 adult sitosterolemia patients (ages 45 and 48 years). By 10 weeks of treatment with cholestyramine (8 g/day), plasma cholesterol levels decreased by 28-38% compared to baseline, plasma sitosterol and campesterol levels levels by 15-34%, and plasma cholestanol levels normalized.
4. Miettinen (ref. 16): Treatment of a 32 year old male with diet and cholestyramine (12 g/day for 12 days) for sitosterolemia reduced plasma cholesterol by 21% and plant sterols by 16%.
5. Nguyen (ref. 18): Treatment of a 27 year old female with colestipol 10 g/day for 20 weeks for homozygous sitosterolemia, decreased plasma cholesterol by 24% and plant sterols and 5 α-stanols by 28% compared to baseline.
6. Parsons (ref. 22): 6 months treatment with a low plant sterol diet did not change total plasma, VLDL or LDL cholesterol in a 48 year old male with β-sitosterolemia but did decrease total plant sterols by 37%. Compared to diet alone, within 10 days of

instituting cholestyramine therapy (8 g/day), plasma total sterols declined by 46%, cholesterol by 52% and plant sterols by 13%. A further decline was evident in each of these variables by week 8 of 24 g/day cholestyramine, followed by a subsequent long-term plateau. The final reduction in total and individual sterols (cholesterol, β-sitosterol, campesterol and stigmasterol) 12 months after adjunct cholestyramine therapy, as compared to the end of the diet-treatment phase, was 66-75%. With the addition of cholestyramine, total plasma and LDL cholesterol declined by 64% and 76%, respectively. A 90% decline in apoprotein B levels were observed within 12 weeks of resin therapy. Xanthomas, angina pectoris and intermittent claudication resolved during 18 months of diet and cholestyramine therapy.

7. Salen (ref. 27) evaluated the effect of cholestyramine on plasma sterol concentrations in 4 patients with sitosterolemia. After treatment with up to 12 g/day of cholestyramine for at least 1 month, plasma cholesterol and sitosterol levels decreased by 45%; and plasma campesterol and 5α-saturated sterols by 55%.
8. Shulman (ref. 31): The addition of cholestyramine (16 g/day) to a low cholesterol diet in a 31 year old female with β-sitosterolemia and xanthomatosis, led to an additional decline of 24% in plasma cholesterol and 38% in LDL-C.

In summary, the efficacy of bile-acid sequestrants in the treatment of 12 patients with sitosterolemia was described in the above reports. In most cases, patients received cholestyramine 8-16 g/day for up to 10 weeks. On patient received cholestyramine 8 g/day for 12 months and one patient received colestipol 10 g/day for 20 weeks. Resin therapy was reported to effect reductions in total cholesterol concentration ranging from 21-64%; plasma sitosterol, 15-45%; campesterol, 15-55%; total sterols 13-75%; LDL-sterols, 41%; and 5α-saturated sterols, 28-55%. Therefore, the efficacy of resin therapy is quite variable but is detectable as early as after 12 days of treatment.

Baseline demographics:

As indicated in the table below, 5 subjects (13.5%) were <18 years of age. The majority of the subjects were female and Caucasian.

Baseline demographics: Intent-to-Treat Population (ITT)		
Characteristic	Placebo (n= 7)	Ezetimibe (n= 30)
Age:		
<18 years	1 (14%)	4 (13%)
≥18 years	6 (86%)	26 (87%)
Sex:		
Female	6 (86%)	18 (60%)
Male	1 (14%)	12 (40%)
Race:		
Caucasian	6 (86%)	27 (90%)
Asian	0	1 (3%)
Hispanic	1 (14%)	2 (7%)

As indicated in the following table, 5 subjects (14%) were washed off of resin therapy prior to randomization, but after entry into the study. During the study, 10 subjects (27%) were on bile salt binding resin treatment.

	Placebo (n= 7)	Ezetimibe (n= 30)
Concurrent treatment of sitosterolemia:		
None	2	12
Yes	5 (statins: 1, resins: 2 and ileal bypass surgery: 2)	18 (statin 6, resins:7, statin + resin: 1; ileal bypass surgery: 3 and apheresis: 1)
Bile salt binding resin therapy:		
not rx'd with resins (stratum II)	3	19
washed-off resins (stratum II)	2	3
continuing resins (stratum I)	2	8

Baseline sterol concentrations are provided in the following table. Because plant sterols and cholesterol are not distinguished in enzymatic assays of cholesterol, both specific LDL-C (via ——————— and LDL-sterols (by ——— assays for cholesterol) were measured.The mean LDL-C at baseline was ~95% of the LDL-sterols, indicating that ~15% were in the form of plant sterols in these subjects.

Baseline Values for Lipid Variables: Modified Intent-to-Treat Population (excludes the 1 subject randomized to the ezetimibe group who was on apheresis therapy)		
Lipid Variable (mg/dl)	Placebo (n= 7)	Ezetimibe (n= 29)
Sitosterol:		
Mean	18.5	21.0
Median	17.6	20.8
SD	9.4	6.7
Min-Max	——	——
Campesterol:		
Mean	9.7	11.0
Median	9.6	11.5
SD	7.4	3.9
Min-Max	——	——
LDL cholesterol:		
Mean	103.3	110.9
Median	89.1	95.3
SD	58.1	64.5
Min-Max	——	——
LDL Sterols:		
Mean	119.9	130.9
Median	86.5	125.3
SD	96.7	66.9
Min-Max	——	——
HDL Sterols:		
Mean	48.9	55.0
Median	51.0	56.0
SD	8.4	12.4
Min-Max	——	——
HDL cholesterol:		
Mean	33.3	39.8
Median	33.9	40.2
SD	6.4	10.5
Min-Max	——	——

Triglycerides:		
Mean	175.9	193.1
Median	195.0	147.5
SD	78.3	148.6
Min-Max		
Total Sterols:		
Mean	204.1	216.8
Median	175.0	210.5
SD	91.7	65.3
Min-Max		
Total cholesterol:		
Mean	144.6	168.0
Median	134.4	167.8
SD	47.9	54.7
Min-Max		
Apo A-1:		
Mean	146.7	159.0
Median	154.0	156.5
SD	24.1	31.9
Min-Max		
Apo B:		
Mean	128.2	129.9
Median	107.0	123.0
SD	75.4	49.3
Min-Max		
Non-HDL Sterols:		
Mean	155.1	161.8
Median	137.5	159.0
SD	87.6	65.2
Min-Max		

Compliance with the diet:
Only 1 subject at one time point indicated non-compliance with the diet.

Protocol P01417: Long-Term (Up to 24 months) Open-Label Extension of P01030: Mean Percent Change From Baseline to Endpoint in Calculated LDL-c for Patients Participating in Both P1030 and P1417:

	Statin 80 mg N= 12	Eze + Statin 40/80 mg N= 29
Study P1030:		
Mean baseline (mg/dl)	384.25	334.25
Mean endpoint (mg/dl)	344.25	253.0
Mean % Δ from baseline to endpoint	10.41%	24.31%
Study P1030:		
Mean baseline (mg/dl)	384.25	334.25
Mean endpoint (mg/dl)	248.83	246.79
Mean % Δ from baseline to endpoint	35.24%	26.17%

LONG-TERM, OPEN-LABEL EXTENSION TO STUDIES P00474 AND P00475: P00476:

Treatment Received in Protocols P00474, P00475 and P00476: Number (%) of Subjects: Interim Reporting Data Set:

Disposition	Placebo	Ezetimibe	Grand Total
P00474 and P00475			
Rec'd randomized rx. assignment in double-blind phase of P00474 or 00475	**431**	**1,288**	**1,719**
Completed double-blind phase	402	1,180	1,582
Discontinued from double-blind phase	29	108	137
P00476			
Participated in P00474 or P00475 and P00476 (therefore, treated with ezetimibe +/- statin in P00476)	**336**	**977**	**1,313**
Treated with ezetimibe alone in P00476	208	575	783
Treated with ezetimibe + statin in P00476	128	402	530
P00474/P00475/P00476 long-term experience			
Total assigned ezetimibe in P00474 or P00475 or rec'd ezetimibe in P00476			**1,624 (100%)**
Statin added in P00476			530 (33%)
Pure ezetimibe monotherapy subset			1,094 (67%)

Disposition in P00474 or P00475	Disposition in P00476			Total: Number of Subjects Participating in P00474 and P00475 +/- P00476
	Did not participate in P00476	Participated in P00476		
		Ezetimibe only	Ezetimibe + Statin	
Placebo	95	208	128	431
Ezetimibe	311	575	402	1,288
Total	406	783 ↘	530 ↙	1,719
		1,313		

Comments on above table:

A total of 1,719 subjects received randomized treatment assignment in the double-blind phase of P00474 and P00475. Of these, 1,313 subjects also participated in P00476 and 406 subjects did not. The combined exposure to ezetimibe with or without statin in these 3 studies was 1,624 subjects (311 + 1,313) with 1,094 subjects (311 + 783) receiving only ezetimibe and 530 subjects, ezetimibe + statin.

Of 1,313 subjects who participated in P00474 or P00475 and P00476, target LDL-C levels were achieved with ezetimibe alone in 783 (59.6%) subjects (208 subjects who had received placebo in P00474/P00475 and not achieved in 530 (40.4%) subjects (128 having previously received placebo and 402 having previously received ezetimibe).

3 subjects received both lovastatin and simvastatin during the study but not simulataneously. One of these subjects inadvertently received simvastatin for 2 days rather than lovastatin and, another received lovastatin for 53 days before the dispensing error was realized. The remaining patient received randomized treatment assignment to

simvastatin which was administered for 5 months but then switched to lovastatin due to fatigue which was reported as an adverse event. This patient took lovastatin for 5 months before data cut-off for interim analysis.

The Interim Report for P00476 comprised 795 male and 829 female subjects, aged 18-86 years, who had hypercholesterolemia characterized by plasma concentrations of direct LDL-C from 104.3-256 mg/dl.

C. Labeling Recommendations:

WITHHOLD 16 PAGE (S)

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LABELING

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